A Down To Earth
PUBLICATION



ANTIBIOTIC RESISTANCE

BODY BURDEN

STATE OF INDIA'S HEALTH

Human and economic cost of antibiotic resistance | Antibiotic residues in food and environment | Antibiotic resistant hospital infections

Antibiotic resistance can undo historical gains made in modern medicine to control diseases. Microbes have become resistant to antibiotics, and Big Pharma has stopped funding research to find new antibiotics due to low returns. The magic bullet—that antibiotics were commonly called earlier—have stopped performing miracles. It is estimated that 10 million people will die each year by 2050 due to antibiotic resistance. India is the top consumer of antibiotics in the world. It is also known for indiscriminately using them and this is leading to resistance. From being used to treat diseases in humans to unmonitored usage as growth promoters in animals and in crops, antibiotic residues are present everywhere in our environment—water, hospitals, houses and even in the food that we eat. *Body Burden: Antibiotic Resistance* unravels a public health crisis in India that has become a nightmare.

This book is the third edition of our *Body Burden* series, State of India's Health. The earlier ones were on Lifestyle Diseases and Con
Diseases.





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CONTENTS

ANALYSIS | OPINION | LIFEHACKS | INSIGHT | DATA

FOREWORD BY SUNITA NARAIN 06





CRISIS OF RESISTANCE

ANALYSIS Microbial rebellion 09
Millions of people are dying from infections that are resistant to multiple antibiotics

INSIGHT The journey of antibiotic resistance 18
The changing character of microbes

LIFEHACKS Routes to resistance 26
How to stop development of resistance

OPINION Expanse of expenses 28
Treatment of antibiotic resistant diseases pushes people into poverty

BODY OF EVIDENCE 31

Data on antibiotic resistance

OPINION Lack of access 52
Shortage of first-line antibiotics affects access to treatment

INSIGHT Swelling cost 56
Long-term economic impacts of antibiotic resistance

RESIDUES AROUND US

ANALYSIS Transmission factor 61
Antibiotic residues in the environment could lead to resistance in microbes

INSIGHT Disposal sans scrutiny 74
With no regulations, unused antibiotics are dumped in the open

LIFEHACKS Hidden dangers 78
How to identify household items with antimicrobials

OPINION A necessity we ignore 80
Technologies to manage antibiotic residues are needed

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HOSPITAL ACQUIRED INFECTIONS

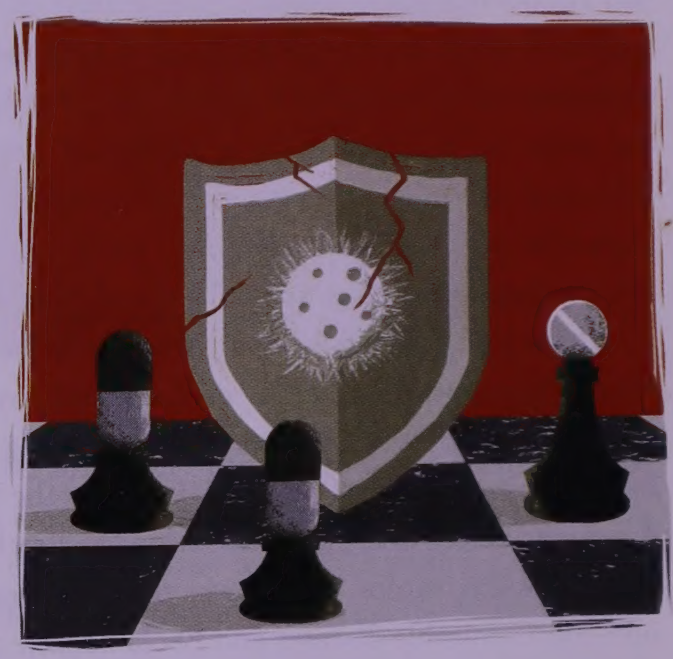
ANALYSIS Diseases inside hospitals 107
The temples of healthcare have become infested with infections

INSIGHT Machines cannot detect inaction 116
Affordable devices to detect bacterial infections are being developed

LIFEHACKS Hospitals that heal 120
How to check if your hospital is safe

OPINION Dearth of data 122
Without comprehensive data, we cannot develop health protocols

INSIGHT The search for alternatives 126
New antibiotics are waiting to be discovered



ANTIBIOTICS ON THE PLATE

ANALYSIS Antibiotics in our food 83
Used as growth promoters, these chemicals have entered the food chain

LIFEHACKS Unexpected exposure 96
How to avoid foods that may have antibiotic residues

INSIGHT Growing resistance 98
Antibiotics are used in food crops

OPINION Safer options to antibiotics 104
Poultry farmers have cost effective alternatives



POLICY FOR CHANGE

ANALYSIS Fighting resistance 133
Policy action to clean environment can reduce resistance

OPINION What should we do? 142
The "One Health" approach that includes all stakeholders is the way

LIFEHACKS Be smart, use less 148
How to reduce exposure to antibiotics

INSIGHT Microbe matrix 150
There is a need to live symbiotically with the microbe

ABOUT THE AUTHORS 154

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DON'T COMPROMISE

The only way to combat antibiotic resistance is to keep the environment clean

SUNITA NARAIN

IT IS a resistance that is difficult to control. Think of it like the revenge of the microbe—the bug that we thought we had conquered and squashed. The miracle of modern medicine, antibiotics—which has saved millions of lives over generations—could be compromised. Why? Because the bugs against which these medicines work have developed resistance. This is a global pandemic and will jeopardise our health and well-being. It will be impossible to treat simple infections, forget life-threatening diseases.

This is a problem of huge proportion—it's the climate change aproportionate crisis of the health world. In 2016, antibiotic resistance became a concern big enough for the United Nations (UN) to discuss it at the General Assembly. Before this, the UN in its long history had discussed health topics only three times—when HIV, non-communicable diseases and Ebola became a global crisis. The Secretary General set up the Interagency Co-ordination Group (IACG) on Antimicrobial Resistance to formulate a blueprint to fight this problem. Over the next two years, discussions between policymakers, industry, individuals and civil society took place. A total of 18 countries commented on the first set of IACG discussion papers. For the second set of IACG discussion papers, 13 countries commented. IACG, in one of its discussion papers, pointed out that antimicrobial resistance in the environment is a challenge and there is a need to better understand resistance in the environment; the root causes and the means to prevent and mitigate the spread of resistance in the environment.

The group finalised its report in April 2019 which said that antimicrobial resistance could threaten a century of progress in health and achievement of the Sustainable Development Goals. The report pointed out that efforts to address antimicrobial resistance in the environment lag far behind in attention, advocacy, political commitment, engagement and the evidence base. The report proposed a "One Health" response to the problem as the drivers of antimicrobial resistance lie in humans, animals, plants, food and the environment.

There are two problems here. For one, multisectoral efforts often fail. We have seen this in the case of cleaning of the Ganga river where the industry continues to pollute even as governments put in more and more money to treat the water. We have seen it in the case of air pollution when governments failed to provide enough public transport while the industry pushed private vehicles on the road. Even in the case of antibiotic resistance, implementation would not be easy as misuse is driven by profit. Farmers use antibiotics as growth promoters and prophylactically so that the size of their animals is bigger. The pharmaceutical industry is pushing antibiotics to increase sales. Doctors are under pressure from the industry to prescribe more and more of these "magic bullets". But there is also the fact that lack of antibiotics can seriously compromise public health. So, people need these medicines—access is as important as the question of misuse. The problem also is that as first-line antibiotics do not bring in profits, Big Pharma has stopped producing them and the market is flooded with second and third-line drugs which are more expensive.

The question is how to ensure that medical practitioners and people know what is "right" for their health. We should ensure that doctors do not over prescribe; people do not misuse. A recent study by Gurugram-based Public Health Foundation of India showed that antibiotics were being prescribed to treat urinary infections which are often self-limiting and respiratory tract infections which are generally viral in nature. The prescription rate of antibiotics in India is 412 per 1,000 persons per year. This is less than other



countries like Italy (957 prescriptions per 1,000 persons), Germany (561 prescriptions per 1,000 persons) and the UK (555 prescriptions per 1,000 persons). However, when it comes to third and fourth-line of antibiotics, India beats others. The percentage of prescriptions with cephalosporins and quinolones (38.2 per cent and 16.3 per cent) in India is significantly higher than in the US (14 per cent and 12.7 per cent). The third-line of antibiotics, which should be prescribed only at the hospital level, are prescribed at the primary care level.

We came face to face with the problem of misuse of antibiotics long back in 2010 when we tested honey for the presence of antibiotics. All honey samples that the Centre for Science and Environment (CSE) tested had residues of at least two antibiotics. Antibiotics were being used by beekeepers to keep their beehives free of disease and as growth promoters. We then tested for antibiotics in chicken in 2014. We did this because a top cardiologist came to us to tell us that he believed something was seriously wrong—this doctor wanted to keep his costs low as heart patients came from poorer and more rural backgrounds. But mortality was high because antibiotics did not control the infections. He believed that exposure to antimicrobials could be through other pathways; not orally administered as medicine, but through food and environment. He wanted us to check.

The CSE laboratory bought 70 samples of chicken from different markets spread across the National Capital Region. It analysed each animal for six antibiotics: oxytetracycline, chlortetracycline and doxycycline (class tetracyclines); enrofloxacin and ciprofloxacin (class fluoroquinolones); and, neomycin, an aminoglycoside. All these antibiotics are critical for humans. These are the same medicines we are prescribed when we are ill—they are life-saving drugs. Of the 70 samples, 40 per cent—literally every second chicken we tested—had antibiotic residues and 17 per cent of the samples had more than one antibiotic present in the muscle, kidney or liver. The antibiotic was delivered through feed—it was given as growth promoter, more than even for therapeutic reasons. Then it was widely sprayed as a prophylactic—to prevent diseases from spreading. All in all, it would make bugs resistant and as it got into the environment and into our food, we would not be able to be treated for diseases. This is a big part of the problem.

But as I found as a member of the Secretary General's IACG, there is huge reluctance to take on the issue—there is opposition from UN agencies who handle live-

stock and food as they believe it will compromise productivity of farms; there is opposition from governments who want unfettered trade in this input food. I was amazed to find that even the issue of growth promoters—when the antibiotic is used to enhance the weight of the animal—and not its use as disease prevention, was stiffly fought by these powerful interests. Finally, it was agreed that governments would adopt measures to stop the use of growth promoters in food production.

But what is also clear is that we need much tougher action. But equally, we need to understand that it is not about the delivery of antimicrobials only. It is also about the way in which we do agriculture or livestock production—we need to make the link with the method and not just the medicine. In the case of antibiotic use in honey, we discovered that the business of beekeeping had been industrialised. In India, the introduction of the European bee (*Apis mellifera*) was done as it was a more prolific producer of honey. This economically viable bee took over the business, virtually replacing the humble but more adapted Indian bee (*Apis cerana*) from our food. At the same time, the business of honey was also transformed. It moved away from small producers, collecting honey from the wild and cultivating honey in natural conditions. It got consolidated into a highly organised business, controlled by a handful of companies. Now it is these companies, who handle all aspects of the trade—from the supply of the queen bee to the paraphernalia of bee-housing, feeding and disease control to the producers, spread across different states. It is an outsourced business, run by franchisees whose job is to find places, like the apple farms of Himachal Pradesh, where there is nectar for bees to suck. The dependence on one introduced species and the emphasis on overproduction means bees are overworked in this competitive business. As disease grows, the answer is to feed bees antibiotics liberally, mixed in sugar and other syrups. The bee makes honey and with it comes the lethal dose of unwanted antibiotics in our food.

It was the same in the case of poultry. This highly organised industry used antibiotics because it was concerned that its chicken bred in overcrowded and often highly unsanitary conditions would get diseased. So, chicken farmers pump antibiotics in drinking water to prevent any outbreaks. Their need to use antibiotics is driven by the method they have chosen to produce our food. This is not all. The poultry industry uses antibiotics also for profit. When chicken is given antibiotic-laced feed, it puts on weight. So, farmers buy antibiotics in bulk and mix it in feed. Or they simply buy the pre-mix feed manufactured by the big poultry, which includes antibiotics and its labels claim that it will promote growth in broiler chicken. So, it is part of the business of our food. This is what we must connect to. We must change.

The good news is that while regulation is necessary, what really triggers change is consumer pressure. Consumer test reports (like ours on honey or chicken) are the key to behaviour change in the livestock industry. Big food giants in the US have now committed to reduce antibiotic in chicken (already done) and now in meat. But not yet for the rest of the world—our lives don't matter it would seem.

This is where our governments must exert pressure. But we need effective antimicrobials more than anyone else. Our recent assessment shows that farmers along the banks of the Yamuna in Delhi, Hisar in Haryana and Fazilka in Punjab use streptocycline (a 90:10 combination of streptomycin and tetracycline) indiscriminately in crops. It is not approved for use in crops. In humans, streptomycin is used for previously-treated tuberculosis (TB) patients, who make up over 10 per cent of the total estimated TB incidence in India. It is also used in multi-drug-resistant TB patients and in certain cases of TB meningitis (brain TB). Resistance to streptomycin is quite high and its large-scale non-human use could add to the problem. The World Health Organization classifies it as a critically important antibiotic for humans.

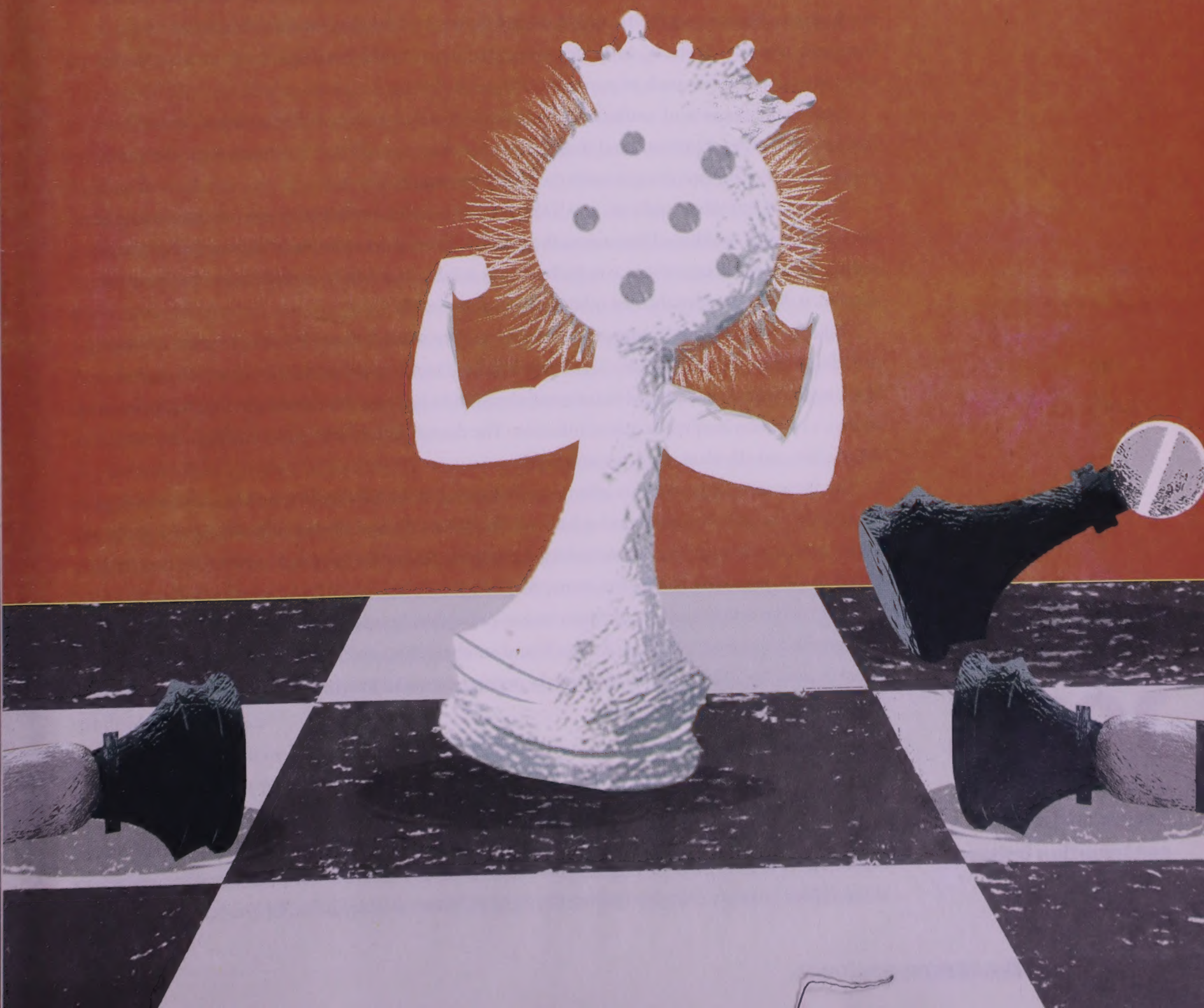
So, this is why we must act. In this coming decade, the revenge of the bug must be understood and combatted. But for this, the "One Health" approach means that we need to fix what is broken—if the water is dirty, it will add to the health burden of people and this will require treatment; if the air is toxic, we will need to take antibiotics and this adds to the problem of resistance. So, let us fix what we can—clean the environment and re-design our food system and fix another of the world's most wicked and existential problems.

As we put together information on antibiotic resistance, we have come to a conclusion that the only way to control the problem is to keep the environment clean.

MICROBIAL REBELLION

Rampant use of antibiotics is changing the character of bacteria and making them resistant. Curing diseases is becoming difficult leading to higher mortality

KUNDAN PANDEY



KAUSHALYA DEVI, a 78-year-old woman from Rani Bagh in Delhi, was admitted in the geriatric medicine ward at the All India Institute of Medical Sciences (AIIMS), New Delhi, in June 2019 for an urinary tract infection. She was suffering from high fever, pain in lower abdomen and increased urination. Treatment began on expected lines: administration of antibiotics. But Kaushalya did not respond to the treatment. Exasperated doctors sent her urine sample to the microbiology department to check whether she is resistant to any antibiotics. The results showed that *E coli*, the culprit behind her infection, was resistant to nine of the 10 antibiotics that were checked. Fortunately, the bacterium was susceptible to the antibiotic, Mitrofurantoin, which the doctors ultimately administered to her.

But not everyone is this lucky. Raghuvar Das, in his late 70s, was admitted to the same department in early September 2019. A resident of Meerut, he was suffering from pneumonia and the bacteria causing his pneumonia was resistant to all of the available antibiotics. "About 32-45 per cent of my patients are suffering from multidrug resistance," says Vijay Kumar, an assistant professor at AIIMS. Das succumbed to the disease on September 19, 2019. Antibiotic resistance (ABR) is specifically used to describe the resistance displayed by bacteria. Bacteria, not humans, become antibiotic resistant and then infect humans and are harder to treat than non-resistant bacteria. Antimicrobial resistance (AMR) is a broad term to describe the resistance of microbes such as parasites, viruses and fungi.

Such is the menace of antibiotic resistance that the department has changed its protocol. Instead of starting treatment and then testing for drug sensitivity if the treatment does not work, they now test for drug sensitivity before starting treatment.

This is not a problem endemic to AIIMS or to New Delhi. Antibiotic resistance is emerging as a disruptive public health problem across the country. There is no estimate of the number of people suffering from the drug resistance in India. While infants and elderly are believed to be the worst affected, it does not mean that the other age groups are safe.

Take the case of Amit Kumar, a 19-year-old student of medicine at R G Kar Medical College in Kolkata, West Bengal. On May 22, 2019, a small red lesion appeared on his leg which started bleeding the next day. It seemed that a small abrasion he had was the entry point for *Staphylococcus aureus*, a common hospital-acquired infection. The doctor prescribed two common antibiotics, amoxicillin and clavulanic acid, for seven days.

But these antibiotics were not effective and the wound started discharging pus after three days. He gave his pus sample for culture on June 10. The results showed the bacteria causing the problem were resistant to four antibiotics, including clavulanic acid that he had taken earlier. The bacterial infection was due to Methicillin Resistance *Staphylococcus aureus* (MRSA), which was found sensitive to four antibiotics, out of which he was prescribed linezolid and mupirocin for five days. Though this lesion began healing, Kumar found another lesion on his face on July 28, which too tested positive for MRSA. He decided to take another course of linezolid and mupirocin and the wound started healing after a week.

103%

was the increase in India's antibiotic consumption between 2000 and 2015

Widespread and spreading

Antibiotic resistance is equally rampant in rural areas too. Ayush, a seven-year-old boy from Surajwasa village of Ujjain district in Madhya Pradesh, lost both his parents to HIV and TB in 2013. In November 2018, Ayush, who now stays with his grandparent, too contracted TB and was taken to the district hospital. After completing the six-month course of medicine, he was termed fit in

More than 58,000 newborns are estimated to die annually due to pathogens resistant to first-line antibiotics, says a study published in 2016

May. However, his grandparents noticed blood in his cough and rushed him back to the hospital. Doctors said that now the treatment would take longer as the pathogen is resistant and the patient must not miss even a single dose, says Rati Lal, his grandfather. "It's tough for us. We have already lost two family members to this disease and we are frightened that the boy might also meet the same fate," says Lal.

Similarly, Semalia Gaund, a 60-year-old resident of Panna district, Madhya Pradesh, has been suffering from TB-like symptoms since 2004. His August, 2019 prescription shows he is suffering from drug resistant TB. But he doesn't know that. He says he is getting treatment for last 15 years, first at the Nowgong Government Hospital in Chhatarpur district of Madhya Pradesh and then at Satna District Hospital. Now, because he cannot travel too long, he is getting treatment at the Panna District Hospital.

A paper published in *PLoS Medicine* in 2016 says that annually, more than 58,000 newborns are estimated to die from *sepsis* due to pathogens resistant to first-line antibiotics. In 2011, *Down To Earth (DTE)* magazine reported the case of Naseem Haider, a taxi driver in Uttar Pradesh's Bijnor. The reporter found Haider in the hospital, watching his 25-day-old son twitch inside the incubator. Born premature, this palm-sized infant, weighing no more than a kg had a feeding tube piercing through one nostril and an oxygen tube through the other. His vital organs were constantly being monitored via wires attached to his body. The baby was born in a private hospital and was given ampicillin, the first antibiotic administered to any premature child to prevent infection. But due to complications (high heart rate), he was shifted to the bigger and specialised Mangla Hospital where he was hooked on to a ventilator that pumped oxygen into his underdeveloped lungs. Three days later he was prescribed cefotaxime, an antibiotic that costs ₹30 per 250 mg, but showed no improvement. Instead, he developed low blood pressure. Investigations showed he had sepsis, a bacterial infection of the blood. Doctors again changed the antibiotic—this time, to meropenem that costs ₹300 per dose.

The baby then contracted pneumonia caused by *Klebsiella* bacteria, which is resistant to all antibiotics except two. "We included polymyxin B and colistin in the infant's regime even though their adverse effects are massive," said his doctor Vipin Vashishtha. "The infant has a slim chance of survival," said Vashishtha, who rues that all the infections were acquired in the hospital itself. "Howsoever well the equipment are sterilised, the chances of infection are high in critical cases," he said. The risk is higher for premature babies because of their weak immune system. Vashishtha had reported 14 similar cases of antibiotic resistance in his hospital between April 2009 and February 2011. So children are extremely vulnerable to the impacts of antibiotic resistance.

Antibiotic resistance is making treatment of infectious diseases like leprosy almost impossible. India has pledged to eradicate leprosy by 2019. Shahla is a 24-year-old who lives in a slum near Delhi's Vijay Nagar area along with her family of eight. In 2007, when she developed skin lesions, she ignored them. The disease remained undiagnosed for two years till she developed numbness in the affected area. Doctors diagnosed leprosy and treated her with multi-drug therapy (MDT)—a specific combination of three pills which takes from six months



Two out of every three healthy persons have antibiotic resistant organisms in their digestive tracts

to a year to kill the leprosy-causing germ *Mycobacterium leprae*. MDT has helped countries significantly reduce the disease burden since its introduction in 1982.

Doctors declared her cured by early 2014, but within six months she developed *erythema nodosum leprosum* (ENL) lesions, a complication of leprosy that can result in deformity. Subsequent blood tests showed that Shahla is resistant to MDT. Doctors at The Leprosy Mission (TLM), an international charitable organisation, are now giving her the second-line of treatment. They say Shahla will take another two years to be cured.

Since 2014, India is a part of a growing list of countries, including Brazil and China, where leprosy can no longer be treated by the conventional MDT. What's worrying is that new patients are now showing resistance to MDT, whereas drug resistance is usually experienced by those who discontinue the treatment. More than 13 per cent of the new cases and 44 per cent of the relapsed cases are showing resistance to rifampicin, one of the three drugs of MDT, say researchers with Stanley Browne Laboratory in Delhi, a WHO centre for surveillance of drug resistance in leprosy. So the options are closing up for patients.

The researchers arrived at this conclusion after diagnosing 215 new and 16 relapsed cases at TLM Hospital between 2009 and 2014. The study was published in *Clinical Microbiology and Infection* in November 2015. "Rising cases of drug resistance since 2014, particularly among new patients, shows that resistant strains are actively circulating in India," says Mallika Lavania, a researcher with Stanley Browne Laboratory.

DR-TB is one of the major emerging public health challenges in India. There are 26,966 multi drug resistant (MDR)-TB patients in India—the highest in the world. While there are 2,130

extensively drug resistant (XDR) TB patients in the country, as per the *India TB Report 2019*, around 10 per cent of patients in India are drug resistant, says Aparna Srikantam, a doctor who is associated with Lepra Society, a Telangana-based non-profit working with TB patients. Srikantam says that generally patients do not understand the difference between TB and drug resistant TB and the importance of adhering to the treatment protocol.

Drug resistant TB (DR-TB) is now prevalent among children. A paper published in *Pediatric Infectious Disease Journal* in December 2018 says prevalence of DR-TB has increased to 9.6 per cent among children affected from TB in Mumbai. It was just 5.6 per cent in 2010, conclude the researchers from Seth G S Medical College and K E M Hospital and BJ Wadia Hospital in Mumbai, Maharashtra.

Patient overflow

Overall, drug resistant diseases are on the rise. A study published in *Infection Control & Hospital Epidemiology* on October 18, 2019, looked at colistin-resistant Klebsiella pneumonia patients admitted to AIIMS between January 2016 and October 2017. Of the 846 isolates, 34 (4 per cent) were resistant to colistin. In total, 22 case-patients were identified. These patients were also resistant to other antibiotics like carbepenems, extended spectrum cephalosporins, and penicillin/B-lactamase. About 45 per cent of these patients died within 14 days.

Recently, the Indian Council of Medical Research (ICMR) published the annual report Antimicrobial Resistance Surveillance Network for January 2018-December 2018. This report is the part of ICMR's efforts initiated in 2013 to enable compilation of data on six pathogenic groups on antimicrobial resistance from the country. This effort aimed to understand the extent and pattern of Antibiotic Resistance (ABR) and also to use this evidence to guide strategies to control the spread of ABR. In the study, ICMR tested samples from 20 top medical institutes from across the country, including AIIMS, New Delhi, Christian Medical College, Vellore and Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh. From these centres, ICMR collected 60,497 isolates in 2018 to check susceptibility of several antibiotics to different bacteria groups like Enterobacteriaceae, Typhoidal *Salmonella*, non-fermenting gram negative bacteria, diarrheal pathogens, Staphylococci and Enterococci and fungal pathogens. The findings were again shocking. Take the case of Enterobacteriaceae. Only half (52 per cent) of the isolates were susceptible to piperacillin-tazobactam. As per the findings, maximum susceptibility was shown against colistin (92 per cent) followed by amikacin (68 per cent) and carbapenems (60-65 per cent).

Drug resistant microbes have been found in healthy people too. A study by ICMR found that two out of every three healthy persons have antibiotic resistant organisms in their digestive tracts. The research, which was published in *Indian Journal of Medical Research* in 2019, shows the scale of rapidly spreading antibiotic resistance in the Indian population. The study was conducted on people living near Chandigarh. It was based on analysis of stool samples of 207 individuals who had not consumed any antibiotics in last one month and also not suffered from any chronic illness.

Lead author of the study, Pallab Ray, a professor of medicine microbiology at PGIMER, Chandigarh, says isolates taken from 130 of the 207 individuals were found to be resistant

Antibiotic resistance is making treatment of infectious diseases like leprosy almost impossible. This, when India has pledged to eradicate leprosy by 2019

to one or more antibiotics. In this study, maximum resistance was noticed against cephalosphorins. Overall, 60 per cent were resistant to it followed by fluoroquinolones (41.5 per cent). Ray says this is a warning sign. The findings show how the healthy human intestinal gut flora has converted into a reservoir of antibiotic-resistant organisms. While these organisms are resistant to low-end antibiotics, but if the misuse persists, it can become resistant to high-end antibiotics as well.

Things are progressively getting worse as was revealed by a report *Antimicrobial Resistance and its Containment in India* published by the Union Ministry of Health and Family Welfare and WHO in November 2016. This report reveals that in last decade, there has been a rapid increase in the proportion of isolates of *Staphylococcus aureus* that are resistant to methicillin. In 2008, about 29 per cent of isolates were of Methicillin-resistant *Staphylococcus aureus* (MRSA), and by 2014, this had risen to 47 per cent.

According to data from the Indian Network for Surveillance of Antimicrobial Resistance (INSAR), MRSA prevalence rate is 41 per cent and showed a high rate of resistance to ciprofloxacin, gentamicin, cotrimoxazole, erythromycin and clindamycin. The report also showed that the emergence of resistance is not limited to the older and more frequently-used classes of drugs, but there has also been a rapid increase in resistance to the newer and more expensive drugs, like carbapenems, which is worrisome. Carbapenems are a class of antibiotics widely considered to be the last-resort antibiotics, which are pressed into use when first and second line treatment options have failed, says the report.

National crisis

Antibiotic resistance may be a global phenomenon, but India is the epicentre of this catastrophe. The country is afflicted by easy access to the strongest of antibiotics without prescriptions or diagnoses. Even qualified doctors and not just quacks prescribe drugs with little thought; overuse in hospitals has created colonies of these superbugs; excessive usage in the livestock sector has contaminated the environment. All this has created a perfect recipe for these super-resistant microbes to menace our health, says Amandeep Aggarwal, a professor at RD Aggarwal Memorial Healthcare, Sangrur. A report by the Centre for Disease Dynamics, Economics & Policy's *The State of World's Antibiotic 2015* provides a glimpse on consumption of antibiotics. India was the top antibiotic consumer in 2010 with 13 billion Standard Units (SUs), followed by China with 10 billion SUs. The US was at third position consuming antibiotics with 7 billion SUs. However, in terms of per capita, the US led in 2010 with 22 SU per person, compared with 11 SU in India and 7 SU in China.

A study published in the *Proceedings of the National Academy of Sciences* in April, 2018, says that between 2000 and 2015, India's antibiotics consumption increased by 103 per cent, the highest in low and middle-income countries. The study tracked antibiotic consumption in 76 countries and also projected the total global antibiotic consumption through 2030. The study says that increase in global consumption of antibiotics (65 per cent)—which is the cause of growing antibiotic resistance—was led by consumption surge in low- and middle-income countries (LMICs). For every 1,000 inhabitants in India, the average amount of antibiotics consumed every day increased by 63 per cent between 2000 and 2015, says the report.

10 million

People will die each year due to antibiotic resistance globally, most of them in India

Authors of the study have underlined their concern saying that the use of last-resort compounds such as glycylcyclines, oxazolidinones, carbapenems and polymyxins are rapidly increasing in all countries. The increase is not just due to human consumption, but also because of overuse in the livestock industry. All these factors point to the fact that we will not know which antibiotics will



Without regulatory scrutiny, it is hard to decipher whether the medicine will do good or harm

work in the future. We don't have a medical protocol. There is a fear that our civilisation can go back to the pre-antibiotic era. A growing list of infections—pneumonia, TB, blood poisoning, gonorrhoea and foodborne diseases—are becoming hard to treat because antibiotics have become less effective or ineffective.

Researchers from Pune-based CSIR-National Chemical Laboratory assessed a cohort of 504 urban Indians for their knowledge, awareness and practice of antibiotic use and antimicrobial resistance. According to the findings, published in May 2018 in *Current Science*, 47 per cent were unaware of the differences between over-the-counter drugs (OTC) and antibiotics. One in four were unaware that dose-skipping could lead to ABR. One in 10 bought medicines without a prescription or started an antibiotic course without consulting a physician.

There is chaos in the market which is leading to a medical crisis in the treatment of ABR. Patricia McGettigan, a reader in clinical pharmacology and medical education, Queen Mary University of London and Allyson Pollock, a professor of public health, New Castle University, the UK, have published a paper in *The Lancet Global Health* in November 2017, where they have highlighted the unprecedented condition of antibiotic sales in the Indian market. Between 2007 and 2012, they found total sales were rising annually and the increase was driven by fixed-dose combinations (FDCs). The most astonishing fact was that they found 118 different antibiotic FDC formulations were available in the market, but only 43 were approved by India's drug regulator, the Central Drugs Standard Control Organization. The sale of unapproved new medicines is illegal in

The Indian government banned some unapproved antibiotic formulations in 2016. But these bans have been challenged by the industry and these formulations are still on sale

India, yet 75 formulations that are being used had no approval. Without regulatory scrutiny, it is hard to decipher whether the medicine will do good or harm.

Unapproved formulations figured prominently in sales figures—270 m units of the FDC antibiotics sold in 2011-12 contained unapproved formulations. The Indian government banned some unapproved FDCs, including antibiotic formulations, most recently in 2016. But the bans have been challenged by the industry and it appears the FDCs remain on sale, write McGettigan and Pollock in *The Conversation*, a news website.

Costly need

When Naseem Haider's newborn baby in Uttar Pradesh's Bijnor was put on polymyxin B and colistin, the family went into a financial crisis. One dose of polymyxin B costs ₹1,400. The infant was given one dose every day. For Haider, hospital expenses alone were between ₹3,000 and ₹10,000 per day. Medicines cost ₹2,000 per day. He had spent over ₹1.5 lakh on his son's hospital stay, investigations and medicines. He had not paid the hospital bill for six days and had already borrowed money from relatives and neighbours. He was resigned to the fate that he would have to take the sick child home and watch him die. A paper published in *Journal of Infection in Developing Countries* in 2014 gives a glimpse of the burden of the antibiotic resistance on individuals. The study, conducted on 220 patients, concluded that the cost of treatment of a resistant bacterial infection to be more than a year's wage of a rural worker. In the study, they found that the median difference between resistant and susceptible groups in overall, antibiotic and pharmacy costs was ₹41,993, ₹8,315 and ₹21,492 respectively. The study says that health consequences such as intensive care admissions, complications, mortality, and length of stay were significantly higher in the resistant group as compared to susceptible group. It is estimated that by 2050, 10 million people will die every year globally due to antibiotic resistance, most of them in India. So how much do we know about antibiotic resistance that is threatening to become a countrywide health crisis?

(Names of patients have been changed to protect identity)

With inputs from Rohan Gupta, Sonal Matharu and Vibha Varshney

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THE JOURNEY OF ANTIBIOTIC RESISTANCE

Research on antibiotic resistance continues to throw up innumerable surprises and shocks. The only way out is to control antibiotic use and its spread in the environment

SHREESHAN VENKATESH

HUMANS HAcolVE long placed immense sanctity in the ability to modify nature, to bend and rearrange her, first for ease of adaptation and then for ease of consumption. Over the course of human history, and especially since the industrial era took shape in the 18th century, this ability has become entrenched in the very idea of what humanness entails. But while humans have busied themselves designing and plotting interventions for the efficient transformation of nature into resources, nature's response too has been building in the background and is gradually spilling over to the fore. Recent years have seen an increased cognisance of the human roots of climate change and the emergence of a new human-influenced geological era- the Anthropocene. However, the first hints that nature was not simply an inanimate object, but an active subject in determining change came more than half a century ago. It was during the same time when most revolutionary advents of modern medicine came to the fore. It is for no small reason that antibiotics are considered one of the most important scientific discoveries ever made. The current range of treatments and life expectancies that go beyond 80 years in some developed nations would be nothing short of miraculous for someone from pre-antibiotic times when a simple cut was grave enough to become an existential threat due to festering infections. But as the "miracle" of antibiotics was taking the world and the microbial universe by storm, this universe too was taking account of the new threat and mapping out its own miracle. The history of anti-biotic resistance or ABR, as it is known today, is perhaps older than the history of antibiotics, and is by no means any less wonderous. A recent research paper claims roots of antibiotics and antibiotic resistance to go as far back as 500 million years.

But in modern records, the phenomena, where microbes—often no bigger than a single cell—can genetically evolve protections against anti-biotic agents, had been observed as far back as the 1950s; warnings though served as little more than the presentation of an appetising new challenge for the human mind to conquer.

Cut to 2019 and ABR has become one of humanity's gravest global concerns and modern medical science seems hopelessly cornered in the decades-long game of evolutionary chess.

Tortoise and the hare

Examples of ancient civilisations controlling microbial infections date back millennia and transcend North Africa, Europe and Asia in



geographic scope. However, the inoculation of antibiotics and the ability to mass produce heralded a revolution in modern medicine. The story of the "accidental discovery" of penicillin—the first antibiotic to be isolated and mass produced in 1928 by Scottish physician Alexander Fleming—is now legend in the retellings of modern science. The story goes that Fleming, while studying the influenza virus at the Laboratory of the Inoculation Department at St Mary's Hospital in London, absent-mindedly left a *Staphylococcus* culture plate outside during a two-week vacation. Upon return, a surprised Fleming found that the mould that had developed on the contaminated culture plate, later determined to be *Penicillum* fungi, was preventing the growth of staphylococci bacteria. The Scot stopped studying Penicillin in 1931, but the work was carried forward by Oxford researchers Howard Flory and Ernst Chain, and the trio was awarded the Nobel Prize in 1945 after the antibiotic became instrumental in cutting the casualties of the Second World War. Within years, antibiotics had become the cure-all silver bullet that had definitively reshaped the face of modern medicine.

Although the Nobel helped cement the legend of antibiotic discovery, none other than Fleming himself forewarned of the epic that would follow. "The time may come when penicillin can be bought by anyone in the shops. Then there is the danger that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug, make them resistant," Fleming had said while accepting the Nobel Prize. And sure enough, within a couple of years, the first recorded case of penicillin resistance was reported from the UK. Soon other prominent figures, particularly from the British and American medical fraternities, began voicing concerns over the dangers of overuse and prophylactic use of antibiotics and its associated risks.

But mere warnings weren't going to dampen the pharmaceutical gold rush that

would ensue. The glut of discoveries of antibiotics after penicillin was enough to instil a sense of confidence among scientists and pharmaceutical companies that no matter what the evolutionary response among the bacteria, an alternative antibiotic was just around the corner. In reality though, scientists had been playing catch up even before they realised a race was afoot.

The emergence of resistance pushed pharmaceutical companies to burn through all the scientific gains of the previous decade. The early 1950s was marked by the entry of "broad spectrum" antibiotics which combined several different simple antibiotic compounds, then came macrolides and fixed-dose combination antibiotics in the mid-1950s and finally came novel synthetically modified agents like methicillin, called beta-lactam antibiotics, in the early 1960s. At the time of its introduction doctors were sure that methicillin would put a halt on the evolution of resistance among bacteria, especially the notorious *Staphylococcus aureus*. It took just a couple of years for this belief to be busted as first case of Methicillin-resistant *Staphylococcus aureus*, or known today as the infamous hospital infection MRSA, was reported from the UK by 1961.

In the early days of the confrontation with antibiotic resistance, medical researchers believed they had zeroed in on the genetic factors and the Darwinian transmission of antibiotic traits. In the first decade of commercial penicillin use, resistance in *Staphylococcus aureus* and *Escherichia coli* bacteria were found to be derived from a specific enzyme penicillinase which effectively inactivated penicillin. The enzyme, initially found only in a few isolates, quickly became a genetic advantage in tackling penicillin. Within a few years, penicillin resistant strains of *S aureus* and *E coli* among other bacteria became the norm. Now we have evidence to show that the origins of these enzymes and the mechanisms they catalyse may go back several millennia before the emergence of pharmaceutical antibiotics. For instance, the beta-lactamase enzymes, which are the most common resistance enzymes in the world, have been traced back millions of years and are a result of random mutations of enzyme-encoding genes which resulted in a spectrum of resistive responses.

Multiple resistance discovery

But in the 1950s, scientists believed that finding a way to work around these enzymes would solve the problem of resistance developing among bacteria. And hence, the introduction of the beta-lactamase-resistant class of antibiotics was supposed to bring an end to the problem of antibiotic resistance. They added a protein to prevent the degradation of the antibiotic agent. This proved to be little more than a hiccup for the bacterium. Instead of producing methicillin-degrading enzymes as scientists expected, methicillin-resistant *S aureus*, which emerged in a few years, produced a novel protein involved in cell wall biosynthesis which provided immunity from the new class of antibiotics. The case of streptomycin, resistance to which gave birth to the resistant strains of tuberculosis was even more puzzling for researchers as mutations not only produced high levels of resistance, but also nurtured a curious dependence among bacteria. Starkly different from clinical results, several researchers in the 1970s found that streptomycin would inhibit protein synthesis in susceptible cells, but was required for proper mRNA development in dependent ones. What this meant was that bacteria were able to modify their own genomic sequences in a way that would enable dependence on antibiotics for propagation rather than annihilation because of them. However, through the unravelling adaptive strategies, confidence among researchers remained high mainly due to the belief that adaptive responses

to antibiotics could only be propagated vertically—inter-generationally.

But this changed when reports from Japan in the mid-1950s suggested that genetic transmission was not just vertical and inter-generational in the Darwinian sense, but bacteria could exchange resistance-enabling mobile genetic agents—eventually named plasmids—with other microbes. Initial western scepticism about the reports turned to horror as medical confirmations from Japan came by the early 1960s. The probability of widespread antibiotics resistance had increased dramatically.

The race was on. For the first time, humans realised that victory was not guaranteed. Researchers realised finally that they were dealing with a complex system of calculated response that involved permutations and combinations at the molecular level. What bacteria, and several other classes of microbes, possess is an exhaustive arsenal of primordial molecular building blocks that could be fashioned in numerous ways to respond to the wide array of threats that they could encounter in natural environments. Imagine a Lego set with unlimited number of blocks of every conceivable shape and size. Theoretically at least, such a situation entails that any structural design challenge would be within grasp and would only hinge on getting the combination of blocks right. Resistance to antibiotic is derived from a repository of molecular building blocks not very dissimilar to the imaginary Lego set, where successful adaptation to any antibiotic component is only a matter of the correct permutations and combinations.

The four pathways

Over subsequent decades, a rich collection of literature decoding the numerous molecular mechanisms enabling resistance among bacteria has emerged, and continues to be actively built on. Scientists have thus far been able to broadly outline four major pathways to resistance through numerous extensively-studied molecular mechanisms-deactivation and/or modification of antibiotics, selective ejection of antibiotic components, protective layering and finally, modification of the chromosomal target sites to make antibiotic components benign, or worse, beneficial. While the categorisation of pathways simplifies the discussion to some extent, the real meat of the matter lies in complex molecular mechanisms and their genetic determinants.

Perhaps the first mechanism to get uncovered was the creation of resistant phenotypes through the overexpression or amplification of specific genes, hidden in bacterial genomes, which are sensitive to antibiotic components. In 1975, scientists VS Kashmiri and Rollin Hotchkiss from Rockefeller University in the US, presented the first evidence of such specific overexpression of genes that were intrinsically resistant to antibiotic agents in strains of *Pneumococcus* bacteria. These were effectively producing resistance to sulphonamides class of antibiotics. The duo showed that *pneumococcus* resistance was intrinsically derived through the amplification of a specific gene already present in the bacteria. While most resistant genes have been found to be recessive and unlikely to result in resistant phenotypes, significant discoveries continue to be made. In 2007, DNA microarray analysis revealed that bacteria *Streptococcus agalactiae* had developed resistance to sulfonamide and trimethoprim classes of antibiotics precisely through such amplification of

When it was clear that antibiotic discovery would not keep pace with the spread of antibiotics, the global community started work on antibiotic resistance in the 1980s and 1990s



specific genes. On the flipside though, genome sequencing of resistant phenotypes has been resulting in the identification of an increasing number of novel RNA target sites for antibiotic action.

Mutations in genes such as those producing the aforementioned enzyme beta-lactamase have been known to produce a wide array of resistive enzymes. Among prominent recent examples of the efficiency of such mutations comes from the case of the flouroquinolones (FQ) class of antibiotics. The introduction of flouroquinolones was expected in some quarters to put a halt to mutative resistance and horizontal transmission of resistant genes since at least two mutations would be required for any such resistance.

The notion was shattered by the early 2000s as FQ resistant bacteria started getting reported in clinics. By the mid-2000s, not only had it become clear that multiple resistive mutations were possible, the exact mechanism of how coordinated mutations had succeeded in modifying bacterial efflux pumps to target FQ antibiotics was understood. Further, mechanisms for horizontal transmission of FQ inactivation have also been outlined where low-level tolerance could buy time for other resistance-enabling mutations.

The possibility of such mutations, and indeed its ubiquity when it came to genes such as those encoding for beta-lactamase enzymes, threw up an important question about the origins of such responses. The fact that bacteria had a wide and adaptive toolkit to push through modifications enabling enzymatic breakdown of specific antibiotics indicated the presence of primordial catalogue of genetic responses that were already present in nature.

This was confirmed in a 2007 paper *The antibiotic resistome: the nexus of chemical and genetic diversity*, where Canadian microbiologist G D Wright showed how a significant proportion of 500 spore-bearing

bacteria (actinomycetes) collected from agricultural, forest and urban soils were naturally resistant to seven or eight of the 21 antibiotics that had been included in the testing. This naturally occurring pool of resistance-enabling genes, now described as the resistome, has been the subject of extensive studies in recent years as scientists look for crucial clues about the origins and scope of AMR in the environment.

A similar pool of genes encoding the ability to subsist on antibiotics, called the "subsistome" was also discovered. A 2008 study on bacterial strains isolated from diverse soil samples showed a significantly high proportion of bacteria with ability to catabolise and digest several common antibiotics including aminoglycosides and fluoroquinolones. In 2018, researchers from the Moscow State University, proposed the existence of a similar "enzystome" that encompasses the tens of thousands of enzymes and their associated resistance encoding genes.

While molecular mechanisms cover one aspect, the other equally critical aspect that has kept researchers busy has been gene transmission. Among the different modes of transmission that have been observed so far such as conjugal transmission, transformation by picking up molecular DNA pieces directly from the environment and even cell-to-cell fusion of bacteria, the one mode that has made medical researchers most jittery is the prevalence of horizontal gene transmission or HGT. In the six decades since HGT was first discovered in Japan, scientists have slowly put together some of the individual components involved in the development of such transferrable mobile genetic units and yet several gaps still remain to be filled.

The first big breakthrough came in 1989, some 30 years after plasmid-mediated transfers were first observed, from a lab in the Macquarrie University in Sydney. Scientists H W Stokes and R M Hall were the first to describe the structure of these "integrons"—essentially isolated bits of DNA which include resistance genes packaged in "gene cassettes" to be used as a kind of exchangeable add-on between bacteria to increase antibiotic resistance. Integrons, although not mobile themselves, have been identified as critical intermediaries in the pick-up and insertion of resistance encoding genes. While the catalogue of integron structures and gene cassettes that have been identified and described has been expanding since their discovery, recent research has also increasingly focused on Integration Sequences (IS) and transposons which are mobile DNA components that have been found to be critical in facilitating gene transmission across several modes.

Still, several gaps remain in the knowledge of the formation of these elements and the exact mechanisms of insertion. While scientists are confident of the involvement of bacteriophages in the evolution of such resistance genes and insertional mechanisms due to the occurrence of "phage fingerprints" in such genes, interestingly enough, bacteriophages with antibiotic resistance genes have rarely been identified in clinical settings over decades of observations. Growing scientific literature on the exact mechanisms and involved components is currently being used extensively in biotechnology and in planning gene-based interventions for plants, animals and humans.

Back in the world of humans, the discovery of the horizontal genetic transmission triggered public debates about the use of antibiotics in livestock farming—as medicine and growth promoters, and over-prescription by doctors—but led only to

Even as public literacy on the flipside of antibiotics was on the rise in the West, the popularity of miracle drugs began to peak in the developing markets

superficial changes in law. While researchers over the next two decades pored over specific mechanisms of resistance and genetic transmission of resistance, new antibiotic discoveries were becoming fewer and further apart. The "Golden Age of Antibiotics" was drying up. Though the period accounts for a majority of the antibiotics in use even today, unfortunately almost none have been impervious to resistance.

Even as public literacy on the flipside of antibiotics was on the rise in the West, popularity of the miracle drugs began to peak in the developing world. With a lack of regulations to contend with, antibiotics began flooding the street and farms in several African and Asian countries. By the late 1980s antibiotic resistance had truly gone global.

Legislative action in India was non-existent until in 2010 when the New Delhi metallo-beta-lactamase enzyme was discovered. The enzyme facilitates resistance to carbapenems

Meanwhile, researchers identified 20,000 possible resistance genes in microbes. Even though only a small proportion of these are functional. Our repository of known active AMR genes has been expanding in recent years, not least due to the immense advantages in data processing from modern machine learning. While a 2010 review lists 21 known active AMR genes, a December 2018 review lists 34 known AMR genes and a further 23 newly-proposed active AMR genes.

As it became clear that antibiotic discovery would no longer keep pace with the spread of antibiotic resistance in the 1980s and the early-90s, the global community, for the first time, began research on antibiotic resistance, which had expanded its scope to other microbes by then and had been rechristened AMR, as a global concern that required coordinated action. The rise of HIV/AIDS epidemics also brought back global attention to infectious diseases, and in a roundabout way to AMR.

By the early 1990s, the World Health Organization (WHO) had started a serious engagement with stakeholders on the issue of antibiotic resistance and hosted a series of high-level meetings addressing what it considered one of the most serious emerging public health concerns for developing and developed nations alike. Years of discussions between multiple stakeholders moderated by the WHO culminated in the "Global Strategy for Containment of Antimicrobial Resistance" in 2001. The document is an important first step in articulating economic and security implications of widespread resistance and drew attention towards the developing situation.

However, legislative action and policy on AMR in India was practically non-existent until the discovery of the New Delhi metallo-beta-lactamase 1 (NDM-1) enzyme in 2010. The enzyme, that facilitates resistance to carbapenem class of antibiotics, has been linked to several cases of heightened multidrug resistance in over 100 countries since its discovery, including in the Norwegian archipelago of Svalbard, nearly 13,000 km from India. In India and around the world, the battle lines have been drawn and the stakes have been evaluated. Researchers have been combing through dirty beards, diving into toothbrush bristles and crouching over toilet seats in their search for new antibiotics. But the options are clear—either control antibiotic use or risk going back to pre-antibiotic times, when surviving past one's 50th birthday was in itself an admirable feat.



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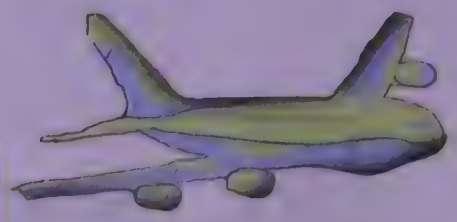
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Routes to resistance

KUNDAN PANDEY lists the various ways microbes become antibiotic resistant and spreads



3

WANDERLUST
Due to international travel, antibiotic resistant microbes, present in human gut, spreads across the globe. The resistance genes too spread in the same way



2

FOOD IMPORTS
Global trade of food products, especially industrially-produced foods can lead to the spread of resistant microbes. Adequate quarantine measures should be set up to identify and avoid them



1

LAX PRESCRIPTIONS
As antibiotics are easily available, people tend to use them indiscriminately. Often, people do not finish the prescribed course of the treatment when they get better and this helps the microbe become resistant





9

GLOBAL WARMING
Climate change has resulted in conditions that allow rapid multiplication of microbes. This provides conditions conducive to the development of resistance



10

OVER POPULATION
When people have to live and work in close proximity, there are more chances of spreading diseases and resistant microbes. Resistant genes accumulate in the environment too



4

POOR INFECTION CONTROL

Lack of vaccination allows microbes to proliferate and become resistant. Many times, patients are not isolated in hospitals and homes, and they end up spreading the disease



5

GROWTH PROMOTION

Large amounts of antibiotics are used for growth promotion in animals reared for food. Poor hygiene measures in areas where animals are housed or among the people who work on farms result in the spread of drug resistant infections





6

AGRICULTURE

Antibiotics are used for controlling bacterial and fungal diseases in crop plants. Residues accumulate in the soil and provide conditions suitable to the development of resistance in soil microbes. Antibiotics are also used to increase crop yield



8

SEWAGE AND EFFLUENTS

Only a fraction of the antibiotic consumed is used by the body. The rest is released in the environment and concentrates in wastewater and sewage. When this water is used in agriculture, it spreads resistance in soil microbes



7

CHEMICALS AT HOME

Many consumer products such as hand washes and domestic cleaners use antibacterial ingredients. These leads to the development of resistance in microbes

EXPANSE OF EXPENSES

An additional 24 million people, most of them in poor countries, will be forced into poverty by 2030 due to costs of hospital visits arising out of antibiotic resistance, says the World Bank

HABIB HASAN FAROOQUI

ANTIBIOTICS ARE key interventions to prevent and control infectious diseases and access to antibiotics is critically linked to health security. However, diminishing antimicrobial effectiveness—antimicrobial resistance (AMR)—represents one of the greatest threats to human health. AMR occurs where a microorganism, previously sensitive to an antibiotic, develops resistance, rendering it ineffective. Though development of resistance is an evolutionary process and is a critical survival mechanism for pathogens, this natural process is accelerated due to the presence of antibiotics leading to the elimination of sensitive microorganisms by the resistant ones. There is sufficient evidence that suggests that an association exists between antibiotic consumption and the subsequent development of bacterial resistance at both the individual and community levels.

A 2015 report by US-based Center for Disease Dynamics, Economics and & Policy *The State of the World's Antibiotics* suggested two trends that contribute to a global scale-up in antibiotic consumption. Rising income is increasing access to antibiotics and saving lives; but consumption is also increasing—both appropriate and inappropriate. This, in turn, is driving resistance. Intensification of food animal production is leading to greater use of antibiotics in agriculture, again driving resistance.

Developing resistance

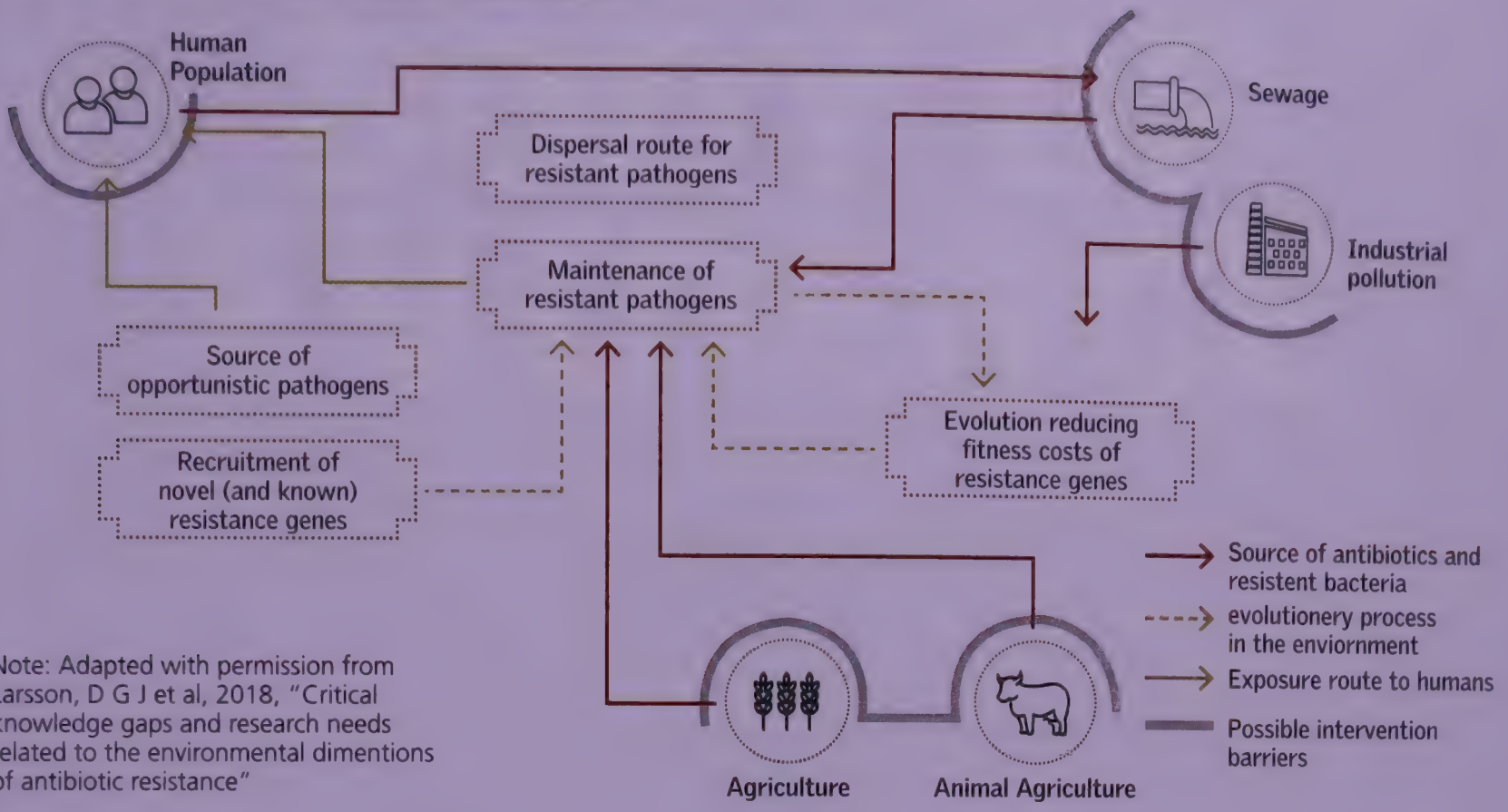
A study published in *The Lancet Infectious Diseases* in August 2014, reported that BRICS countries—Brazil, Russia, India, China and South Africa—consumed 76 per cent of the overall increase in global antibiotic consumption between 2000 and 2010, of which 23 per cent was attributed to India. Of the total medicine sales worth US $12.6 billion in India between 2013 and 2014, antimicrobials contributed to around 16.8 per cent. A significant proportion of these sales were made through out of pocket (OoP) expenditures in the absence of universal health coverage and financial risk protection mechanisms.

India faces a complex situation. On one hand, there is excessive use of newer generation of antibiotics in urban areas and in the private sector, which is potentially leading to AMR, and on the other, there is poor access to antibiotics in rural areas leading to avoidable morbidity and premature mortality. Marcella Alsan of Stanford University and lead author of a study published in *The Lancet Infectious Diseases* in July 2015 has demonstrated that out-of-pocket health expenditures were strongly correlated with antimicrobial resistance in low-income and middle-income countries. The explanation to this lies in the consumer theory—which predicts that raising the price, via high OoP expenditure or high co-payment for public service—will shift more consumers towards the private sector.

Estimates suggest per capita antibiotic consumption in India increased by around

Understanding the battle

How to track and combat resistant pathogens



Note: Adapted with permission from Larsson, D G J et al, 2018, "Critical knowledge gaps and research needs related to the environmental dimentions of antibiotic resistance"

22 per cent between 2012 and 2016. Though antibiotic consumption rates in India are still lower as compared to Europe, there is increasing use of newer class of antibiotics such as carbapenems, 3rd generation cephalosporins and penicillins with beta-lactamase inhibitors.

A study published in *The Lancet* on February 12, 2005, says there are higher rates of antibiotic resistance in countries with high per capita antibiotic consumption. In India, which is one of the top consumers of antibiotics, the AMR data highlights this grim situation. Another study says that more than 70 per cent enterobacteriaceae is resistant to 3rd generation cephalosporins. Among the enterobacteriaceae species, *Klebsiella* and *E coli* have been found to be resistant to 3rd generation cephalosporins (80 per cent).

Earlier, New Delhi metallo-beta-lactamase 1 (NDM-1) conferred carbapenem resistant gram-negative enterobacteriaceae was reported from India. These strains were highly resistant to all antibiotics except to tigecycline and colistin. Though *The Lancet* 2005 study demonstrated a correlation between higher rates of antibiotic resistance in countries with high per capita antibiotic consumption, there are uncertainties about the nature of resistance—temporary or permanent. This could be due to possible causal pathways and the magnitude of resistance over time and the impact of reducing the use of antibiotics on resistance rates. The correlation between antibiotic consumption and resistance rates are confounded not only by multiple pathways of interaction between environment, microorganisms and human beings, but also by prevalence and transferability of resistance coding genes in the pathogens (*see graph*).

This loss of antimicrobial efficacy has become a major health security threat, not only because of high treatment costs for resistant infections, but also because of limited access to topline antibiotics. The situation of AMR is further compounded by the fact that manufacturers have an almost empty pipeline of new antibiotics. The number of antimicrobial agents approved by FDA steadily dropped from 16 between 1983 and 1987 down to just three between 2008 and 2012. Further, many new antibiotics that been introduced in the markets recently are derived from a limited number

of types, or classes, of antibiotics that were discovered by the mid-1980s. So antibiotics can be considered as classic case of "tragedy of commons"—when individuals spoil a shared resource for their self-interest. One way to understand the economic costs attributable to AMR is through production function approach—increased AMR-related mortality would reduce the size of working population, whereas increased AMR-related morbidity would reduce the working population and may also reduce the labour force's efficiency.

Moreover, AMR attributable morbidity of the non-productive members in the family of the labour force may lead to reduced labour supply on account of care provided by family members to their loved ones. This negative impact on the labour supply can be measured in monetary terms as economic

In low-and middle-income countries, out-of-pocket medical expenditures are strongly linked to antibiotic resistant diseases

implications of AMR on global economy. In simple terms, the increased direct healthcare cost on account of AMR can be measured as costs associated with additional investigations, additional treatments, longer hospital stay, whereas other indirect costs would include people not engaging in economic activities by taking longer time off work, reduced quality of life and greater likelihood of death. These can be summarised as the impacts of AMR on society at large—both health and economic.

Studies suggest that in the European Union (EU) alone, the additional burden of AMR is in range of 2.5 million hospital days, 25,000 deaths and economic losses of 1.5 billion Euros due to extra healthcare costs and productivity losses.

A review commissioned by the UK Prime Minister's on antimicrobial resistance highlighted that up to 10 million lives per year could be lost by 2050—up from 0.7 million estimated deaths presently occurring worldwide. Cumulatively, US $100 trillion of economic output is at risk (in some scenarios) due to the rise of drug-resistant infections. A review on estimating the burden of AMR found significant impacts from resistance. Excess healthcare system costs ranged from non-significance to US $1 billion per year, while the economic burden ranged from $21,832 per case to over $3 trillion in GDP loss. A World Bank report suggests that the impacts of AMR on poverty are particularly concerning. In the high AMR-impact scenario, an additional 24 million people would be forced into extreme poverty by 2030 and unfortunately, most of the increase would occur in low-income countries.

The economic impact of increasing AMR rates is now on the top of the global agenda, not only because of health security threats but also because of severe economic consequences. The 68th World Health Assembly endorsed the Global Action Plan on Antimicrobial Resistance (GAP-AMR) in May 2015, which urged member states to align their National Action Plans on AMR with GAP-AMR by May 2017. The high-level meeting on AMR at the United Nations General Assembly on September 21, 2016, has further strengthened the global commitment to address the problem of AMR.

A recent review of the global AMR agenda highlighted the progress in public awareness about AMR, restriction on the use of antibiotics in agriculture, surveillance of AMR and international cooperation. However, three areas where progress is disappointing are: the introduction of market entry rewards to incentivise the development of antibiotics; vaccines against critical new pathogens; and, affordable key point-of-care diagnostics.

BODY OF EVIDENCE

Antibiotic resistance in numbers



Casting a shadow

Antibiotic resistance is amongst the top 10 priority global health threats for 2019, as per the World Health Organization

GLOBAL

Today
0.7 million
people die due to AMR every year

2030
24 million
people will be driven to extreme poverty due to AMR's impact on SDGs

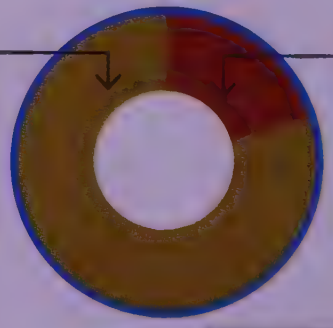
2050
10 million
people will die every year due to AMR, which will cost US $100 trillion to the world

AMR WILL DERAIL 10 SUSTAINABLE DEVELOPMENT GOALS

- Eradicate poverty (SDG 1)
- Spur economic growth (SDG 8 and 12)
- Reduce inequality (SDG 5 and 10)
- Improve global public health (SDG 3)
- Reduce hunger (SDG 2), and
- Protect the environment (SDG 6, 14 and 15)

50 PER CENT OF ANTIBIOTICS USED INCORRECTLY

80 per cent of these antibiotics consumed are either prescribed by healthcare providers or purchased directly by consumers without prescription. Half of this is used inappropriately for coughs and colds that adds to the AMR burden



Only 20 per cent of antibiotics are used in hospitals and other healthcare facilities. Hospitals generate some of the most dangerous and difficult-to-treat infections, a result of heavy use of antibiotics

REASONS BEHIND SPREAD OF AMR

Developing countries

- Lack of surveillance of AMR incidence
- Poor quality of antibiotics
- Clinical misuse
- Easy access to antibiotics

Developed countries

- Poor hospital-level regulations
- Excessive antibiotic use in food-producing animals
- Research on antibiotics is slowing down due to the lack of economic incentives

WORLD'S RESPONSE TO AMR

WHO has rolled out three key strategies: GAP-AMR, a global action plan, GLASS to monitor the action plans and the AWaRE list of antibiotics based on their usage

AWaRE list: Released in 2017, it currently classifies 180 antibiotics into three groups to emphasise the importance of their optimal uses and potential for antimicrobial

Access group
48 antibiotics
Includes antibiotics that can fight a wide range of commonly found pathogens while showing lower resistance potential than antibiotics in the other groups

Watch group
110 antibiotics
Includes antibiotics that have higher resistance potential such as third generation cephalosporins, fluoroquinolones and carbapenems

Reserve group
22 antibiotics
Includes antibiotics that should be reserved for treatment of infections due to multi-drug-resistant organisms. They should be used as last resort options

Source : World Health Organization and Center for Disease Dynamics, Economics & Policy

How bacteria becomes antibiotic resistant

Bacteria resist the effects of antibiotics by using the following genetic strategies, with thousands of variations:

- Produce destructive enzymes to neutralise antibiotics
- Modify antimicrobial targets, by mutation, so that drugs cannot recognise them; Remove antimicrobial agents by pumping them out (efflux)
- Prevent antibiotics from entering by creating a biofilm or otherwise reducing permeability
- Create bypasses that allow bacteria to function without the enzymes targeted by antibiotics

GLOBAL ACTION PLAN ON ANTIMICROBIAL RESISTANCE: In May 2015, the Sixty-eight World Health Assembly adopted the global action plan on antimicrobial resistance or GAP-AMR. The goal of the global action plan is to ensure, for as long as possible, continuity of successful treatment and prevention of infectious diseases with effective and safe medicines that are quality-assured, used in a responsible way, and accessible to all who need them. Today, 100 countries, including India, have developed National Antimicrobial Resistance Action Plans

GLASS: In alignment with the work of the GAP-AMR, GLASS promotes integration with other surveillance programmes in public health and the animal and environment sectors. GLASS facilitates the surveillance of resistance in eight priority bacterial human pathogens, some with links to the food chain. Starting 2019, , it is also monitoring antimicrobials consumption by humans. It has 77 countries, including India

INDIA

0.06 million
neonatal sepsis deaths are attributable to drug-resistant infections in India

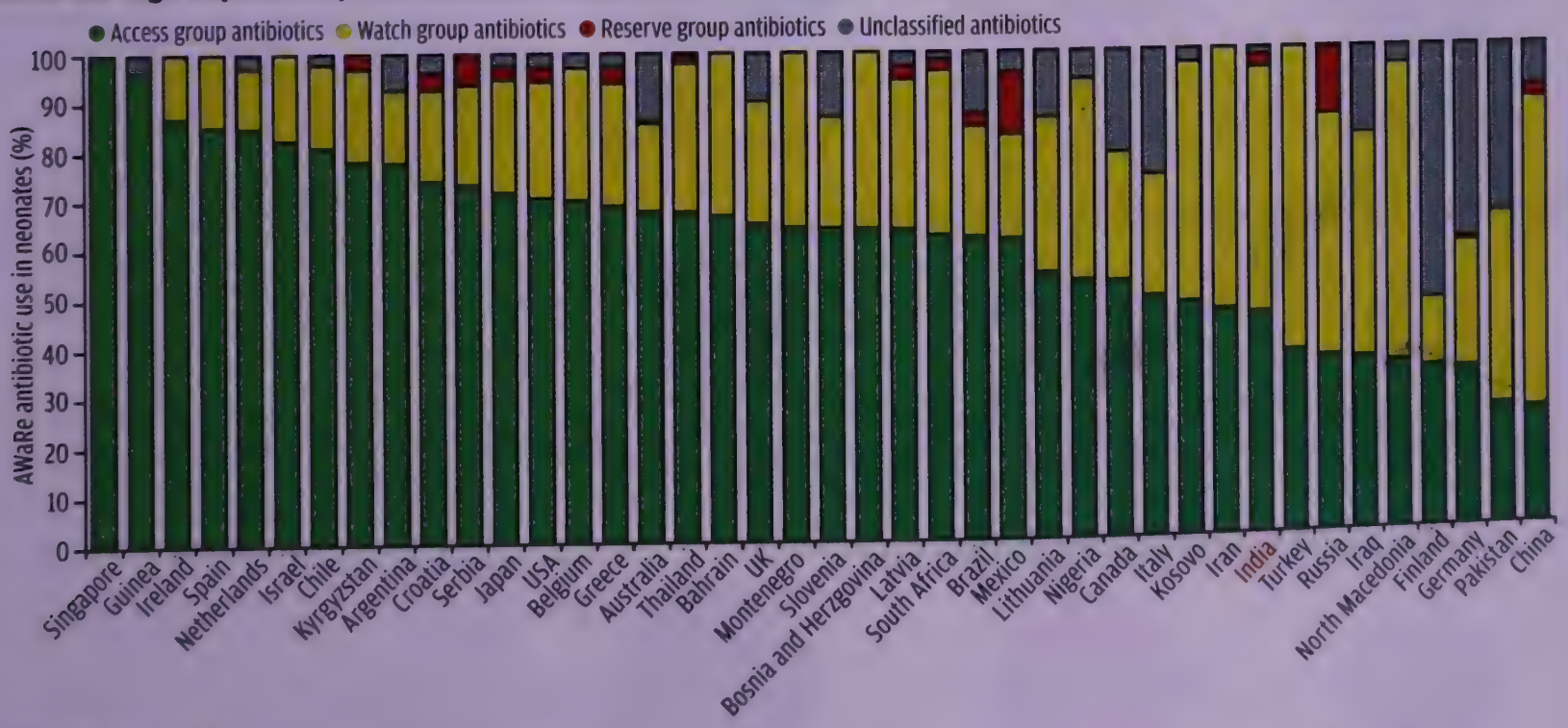
US$ 700
the cost of treating an AMR patient in India. This is equivalent to 442 days of work of a rural male casual worker

103 %
Increase in antibiotics consumption between 2000 and 2015

50 %
antibiotic prescriptions are inappropriate

64 %
antibiotics are sold unapproved

WATCH OUT
India has high dependency on antibiotics classified by WHO under watch and reserve groups



INDIA'S ACTION PLAN
In 2017, India adopted the National Antimicrobial Resistance Action Plans (NAP-AMR) for 2017-2021. It identifies six strategic priorities, of which five are aligned with the Global Action Plan on AMR and the last one focuses on state-level action plans on AMR. The country also has 55 surveillance hospitals, of which 21 provides data to GLASS

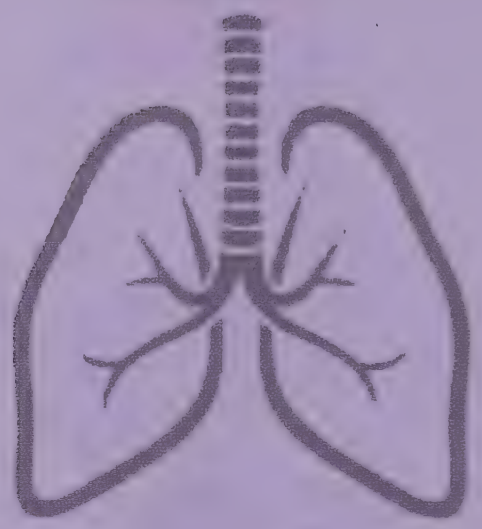
TB or not to be resistant

India's TB burden is on the rise, a trend that does not go well with the country's ambitious plan of becoming TB-free by 2025. The country will also have to fight rising drug-resistant TB cases

10 million
World's TB cases in 2018

130,000
drug-resistant TB cases recorded globally in 2018

8,000
extensively drug-resistant or XDR TB cases recorded globally in 2018



27%
India's share in the global burden of TB, MDR/RR TB and XDR TB, the highest in the world

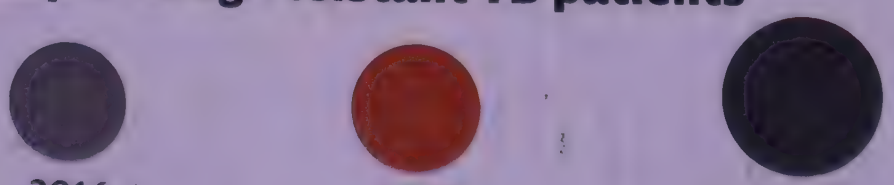
IN 3 YEARS, INDIA RECORDED

23% increase in TB cases



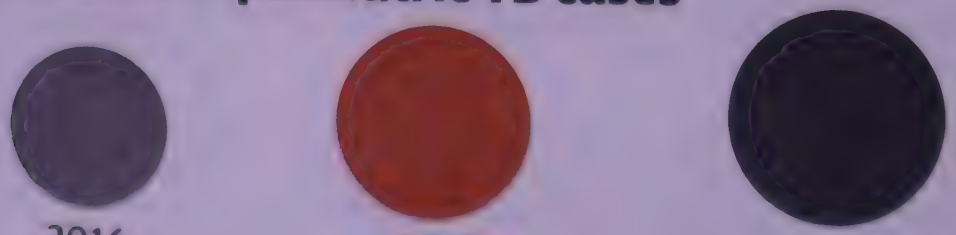
2016 **1.75 million**
2017 **1.83 million**
2018 **2.16 million**

73% jump in drug-resistant TB patients



2016 **33,820**
2017 **38,605**
2018 **58,347**

74% increase in paediatric TB cases



2016 **76,475**
2017 **109,678**
2018 **133,059**

What is tuberculosis

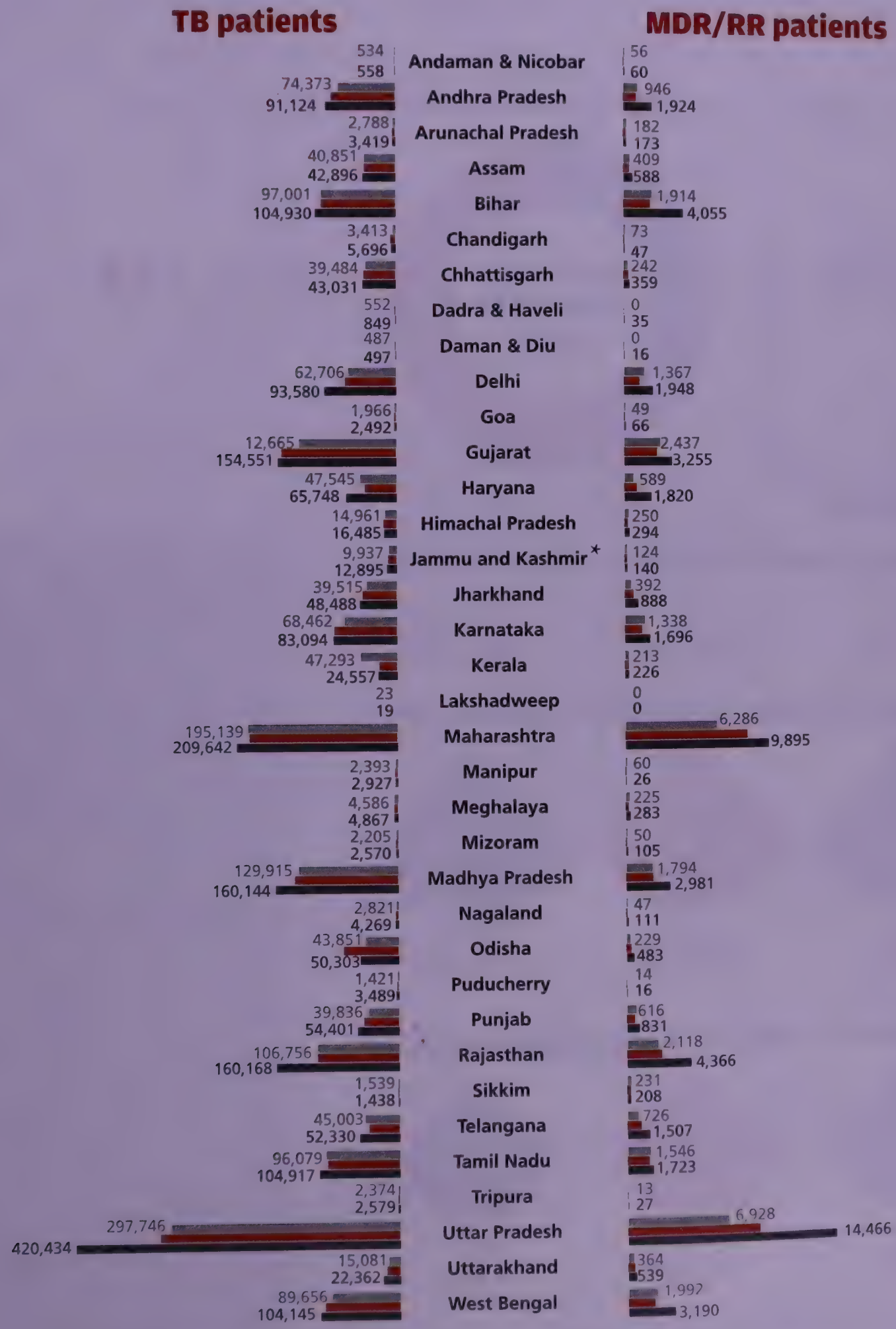
It is caused by an airborne bacterium *Mycobacterium tuberculosis*, which usually attacks the lungs, but can attack any part of the body such as the kidney, spine, and brain

What is drug-resistant TB

M tuberculosis can develop resistance to the antimicrobial drugs used to cure the disease. TB patients can become resistant to drugs if they have not completed the drug course properly or they have been contacted by a TB bacteria from a resistant patient. There are two kinds of resistance:

- Multidrug-resistant tuberculosis (MDR/Rifampicin resistant or RR TB) and extensively drug-resistant TB (XDR TB). Patient diagnosed with MDR/ RR TB does not respond to two commonly used anti-TB drugs: isoniazid and rifampicin.
- XDR TB is a rare type of MDR/RR TB. Besides the above two drugs, XDR TB patients stop responding to fluoroquinolone and at least one of three injectable second-line drugs: amikacin, kanamycin and capreomycin.

STATE OF AFFAIRS | 10 states account for 82 per cent of the drug-resistant TB cases in the country. Uttar Pradesh alone accounts one-fourth of the resistance burden

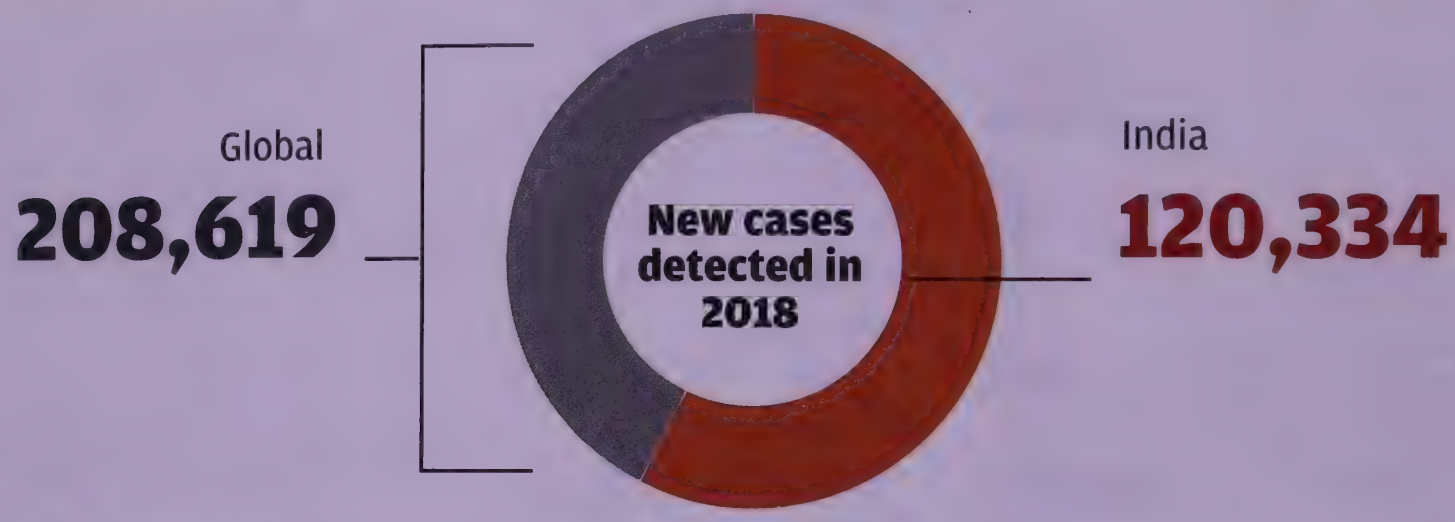


Source: Ministry of Health and Family Welfare and World Health Organization

*Before bifurcation

Antibiotic resistant leprosy

India was declared leprosy free in 2005. Yet, in 2018, the country carried nearly 58 per cent of the world's burden of new cases. The country is a global hotspot of antibiotic resistant leprosy

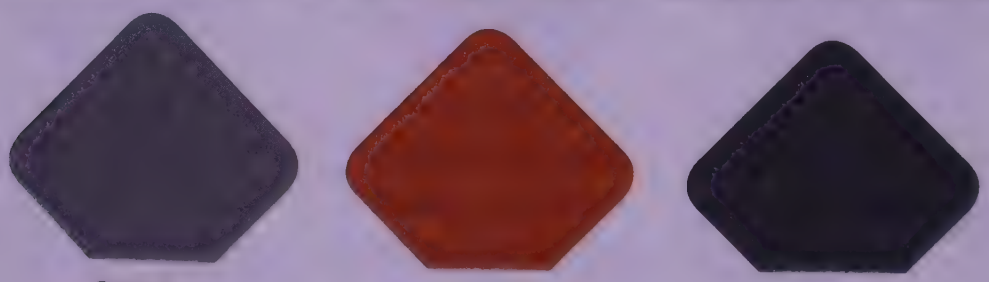


In 3 years

4% DECREASE IN NEW LEPROSY CASES GLOBALLY

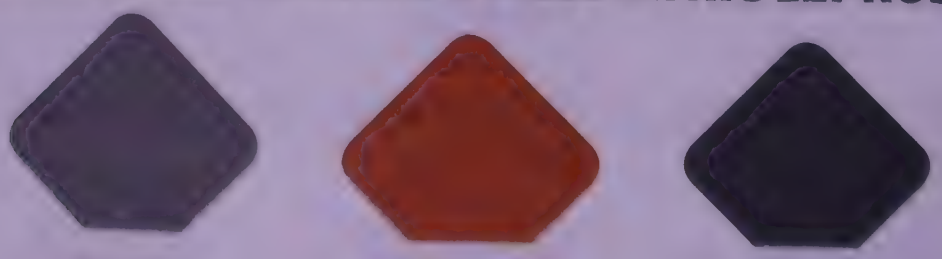
2016	2017	2018
217,971	211,182	208,619

11% DECREASE IN NEW LEPROSY CASES IN INDIA



2016	2017	2018
135,485	126,164	120,334

22% DECREASE IN INDIA'S PAEDIATRIC LEPROSY



2016	2017	2018
11,792	10,287	9,227

Source: National Health Profile 2019 and World Health Organization, August 2019

What is leprosy?

Also known as Hansen's disease, it is a chronic infectious disease caused by *Mycobacterium leprae*. It mainly affects the skin, the peripheral nerves, mucosal surfaces of the upper respiratory tract and the eyes. Leprosy is known to occur at all ages and is curable.

What is drug-resistant leprosy?

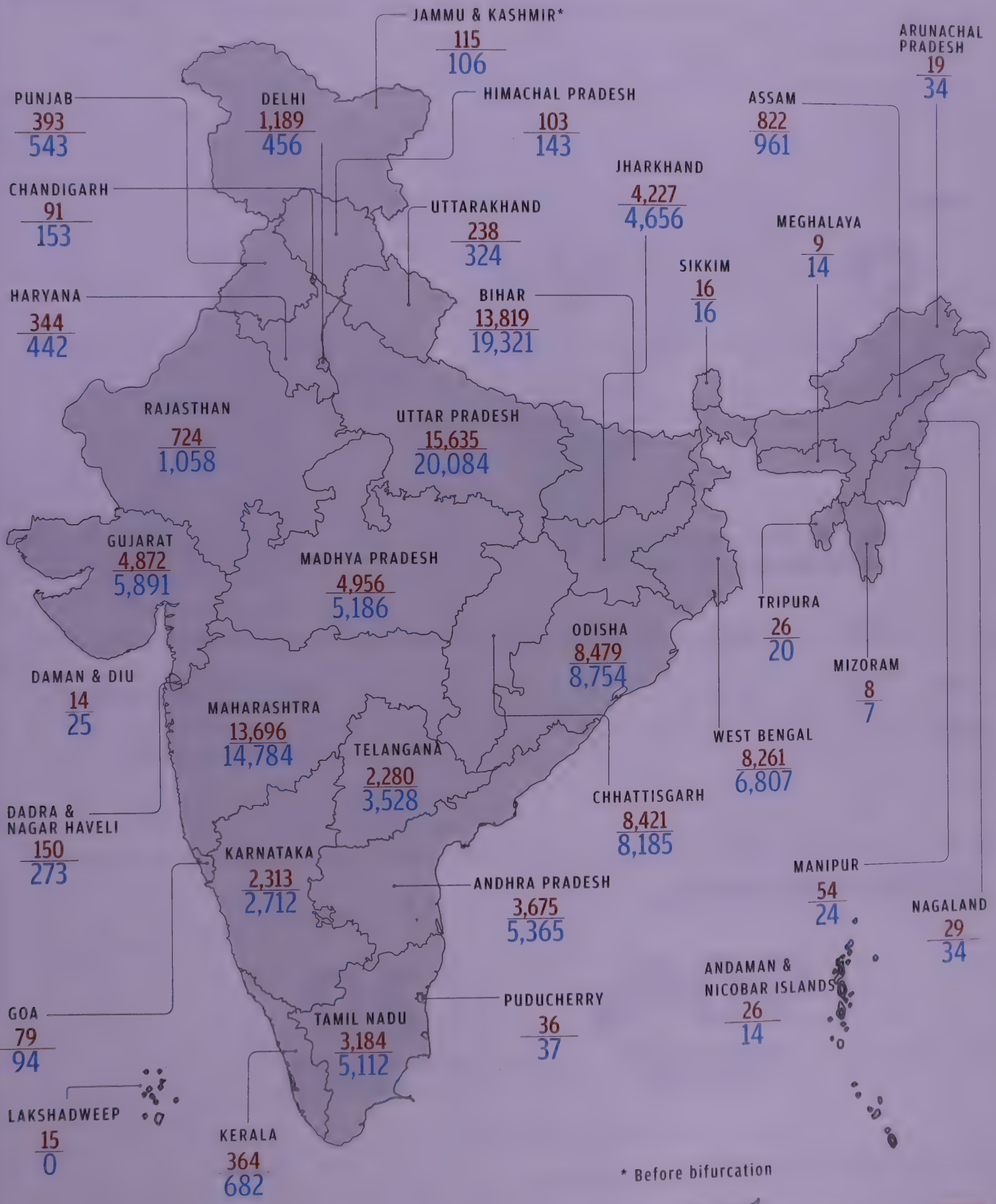
In India, antimicrobial resistance (AMR) in leprosy was first detected in the 1980s when mono therapy was in use. In response, multi-drug treatment was introduced.

A recent World Health Organization study conducted between 2009 and 2015 found drug-resistance in 4.7 per cent of the new leprosy cases. The global study analysed 1,932 new leprosy cases, of which 382 were in India. The global incidence of AMR was 3.8 per cent.

TROUBLED STATES

26 states and Union Territories have registered an increase in new leprosy cases in 2017 and 2018

NEW LEPROSY CASES IN
2017
2018



* Before bifurcation

Carpet bombed by cholera

Cholera cases have increased by 28 per cent between 2017 and 2018 and the disease is spreading to new regions. At least nine studies prove that multiple drug resistant cholera is increasing the burden

Globally

1.3-4 million
Cholera cases recorded every year

0.02-0.14 million
Cholera deaths recorded every year

India saw 28% increase in cholera cases between 2017 and 2018

	2016	2017	2018
Cases	718	508	651
Deaths	3	3	6

A study conducted on 443 cholera-causing *Vibrio cholerae* strains taken from patients in Kolkata and Delhi between 2008 and 2019 found

99%
strains were resistant to two or more antibiotics

17.2%
strains were resistant to 10 antibiotics

7.5%
strains were resistant to 14 antibiotics

Source: Translational Health Science and Technology Institute, Faridabad, Haryana

GLOBAL AMBITIONS...

90%
Reduction in cholera deaths by 2030

20
countries to eliminate cholera by 2030

Source: National Health Profile 2019 and World Health Organization

NEW HOTSPOT

Gujarat is the only state that has recorded an increase in cholera cases between 2016 and 2018



What is cholera?

It is an acute diarrhoeal disease caused by bacterium *Vibrio cholerae*. Patients are usually administered fluids for rehydration and are given antibiotics in extreme cases

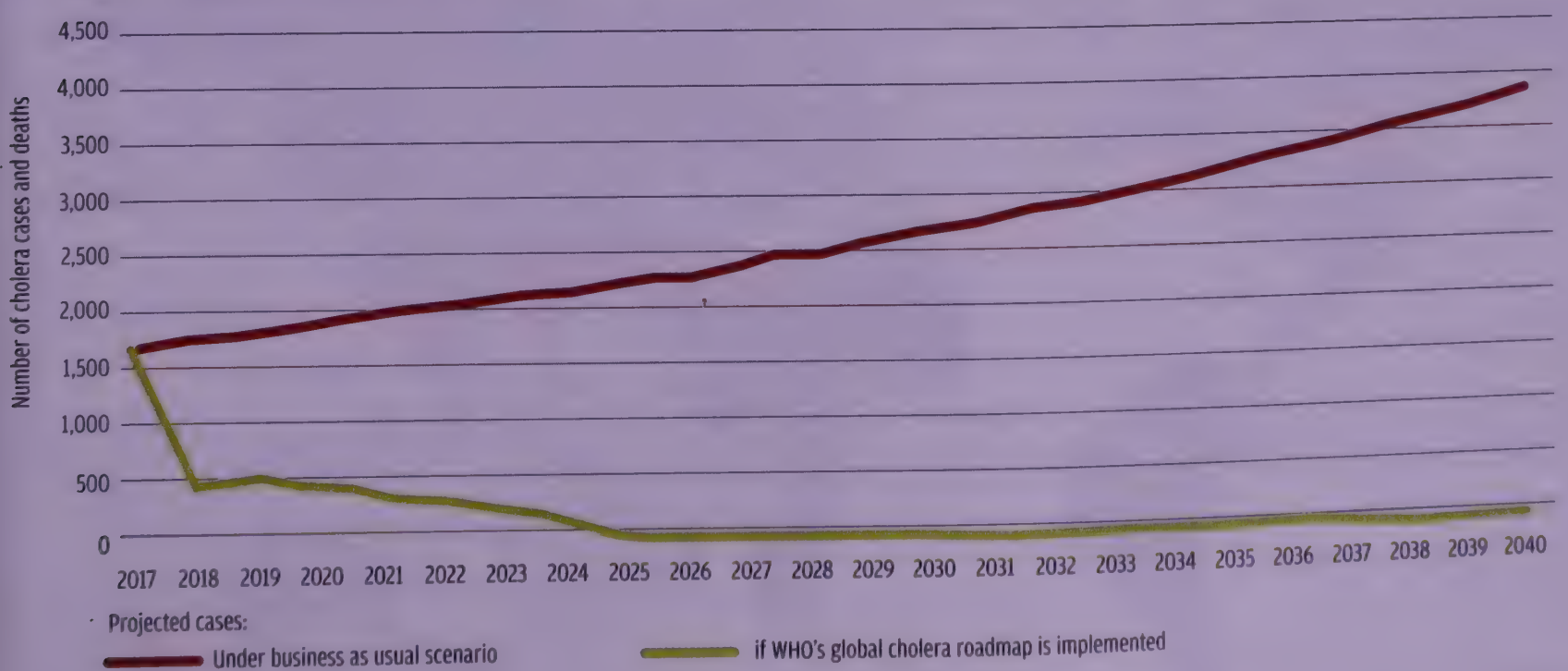
Increasing severe heat waves and intense flooding due to climate change is likely to spur the spread of cholera rapidly.

What is drug-resistant cholera?

Studies have shown resistance to anti-cholera drugs such as imipenem and spectinomycin rifampicin and ciprofloxacin.

...DEMAND ACTION

Cholera burden in the world will continue to rise, more than doubling in the next 20 years under business as usual scenario



Typhoid tyranny

India contributes 16 per cent of the global typhoid burden, a disease which has high prevalence of drug resistance. The country is yet to maintain a registry



	GLOBAL (2017*)	INDIA (2018)
CASES	14.3 million	2.3 million
DEATHS	0.14 million	399

*Latest global data is available till 2017

What is typhoid?

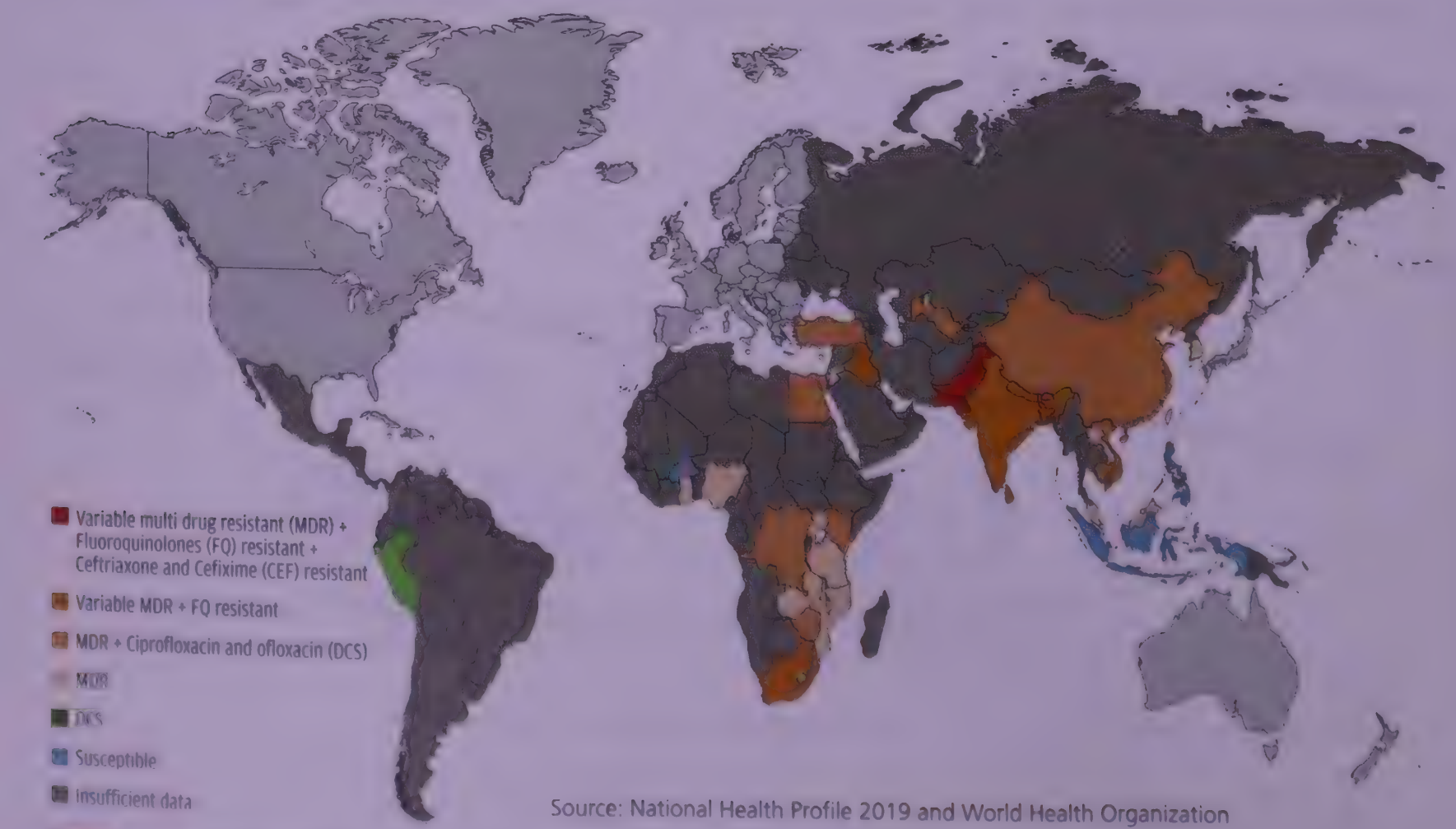
It is an infection caused by the bacterium *Salmonella typhimurium*, which lives in the intestines and bloodstream of humans. It spreads between individuals by direct contact with the feces of an infected person.

What is drug-resistant typhoid?

Multidrug-resistant (MDR) *S typhi*, defined as strains resistant to ampicillin, chloramphenicol and cotrimoxazole, developed and increased in frequency from the 1990s. Following the increase in MDR *S typhi*, treatment practices shifted to the use of fluoroquinolones. However, over the past 30 years, there have been reports of continuous resistance in fluoroquinolones in Asian and African countries (see map). Recent studies have also shown high resistance to ciprofloxacin.

CONSTANT THREAT

S typhi has grown resistant to even third generation drugs such as ciprofloxacin



Source: National Health Profile 2019 and World Health Organization

PAN INDIA PROBLEM

16 states and Union Territories have recorded increase in typhoid cases between 2017 and 2018

Deaths due to typhoid (enteric fever)

Cases due to typhoid (enteric fever)

XXX 2017 XXX 2018

JAMMU & KASHMIR*
0 45,845
0 40,000

ARUNACHAL PRADESH
0 3,553
0 2,456

PUNJAB
0 37,896
0 55,239

DELHI
17 18,368
20 27,132

HIMACHAL PRADESH
12 39,692
5 25,821

ASSAM
122 15,137
83 16473

CHANDIGARH
1 11,531
0 13,158

JHARKHAND
0 41,685
0 36,272

UTTARAKHAND
7 32,367
4 33,685

MEGHALAYA
0 7,893
0 7,466

SIKKIM
0 104
0 158

HARYANA
4 48,581
7 55,698

BIHAR
2 171,281
1 129,622

RAJASTHAN
0 79,017
0 87,751

UTTAR PRADESH
248 650,192
224 764,272

GUJARAT
0 41,794
1 56,390

MADHYA PRADESH
9 108,759
3 72,805

TRIPURA
4 2,836
2 3,664

ODISHA
15 58,935
7 52,765

MIZORAM
1 2,537
0 3,387

DAMAN & DIU
0 480
0 615

MAHARASHTRA
0 95,814
9 114,559

WEST BENGAL
8 238,569
17 251,296

TELANGANA
0 54,695
0 51,145

CHHATTISGARH
3 71,321
4 60,164

DADRA & NAGAR HAVELI
1 7,820
0 9,246

KARNATAKA
4 137,973
0 127,150

MANIPUR
0 4,184
0 3,483

ANDHRA PRADESH
17 163,929
7 148,490

NAGALAND
6 9,483
0 9,089

ANDAMAN & NICOBAR ISLANDS
0 664
0 640

PUDUCHERRY
0 1,596
2 1,307

GOA
0 346
0 530

TAMIL NADU
14 49,806
1 44,316

LAKSHADWEEP
0 111
0 57

KERALA
0 2,561
0 2,234

* Before bifurcation

Magnitude of meningitis

India shares nearly 18 per cent of the global meningitis burden. A recent study in India found antibiotic resistance in close to 60 per cent of children suffering from the disease

Global (2016)

2.82 million
cases

0.32 million
deaths



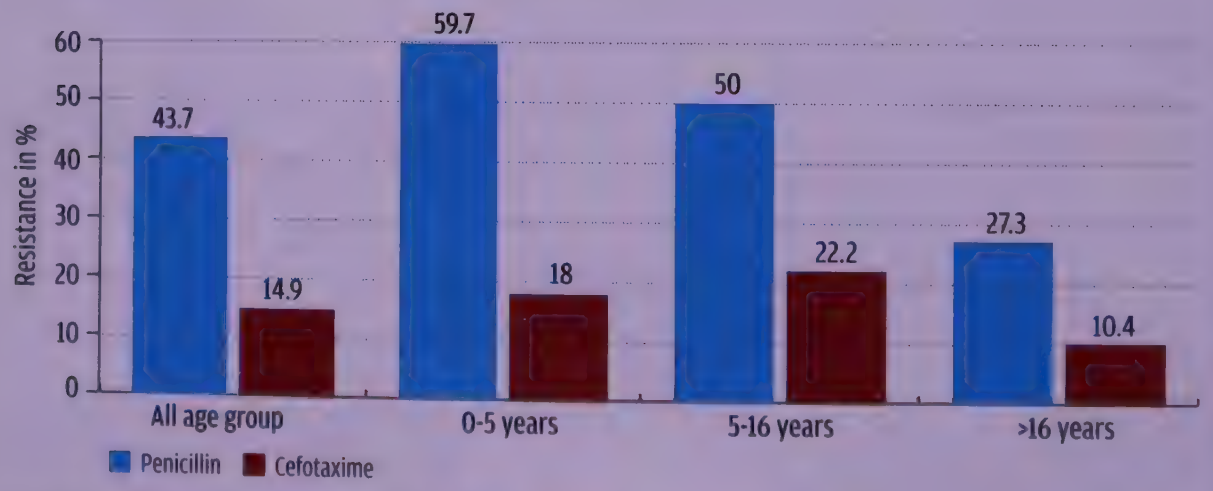
India (2016)

0.5 million
cases

0.06 million
deaths

YOUNG THREAT

AMR is most prominent in children below 16 years



WORSE WITH TIME

There is a steady increase in resistance of meningitis in both penicillin and cefotaxime



What is meningitis?

Meningitis is a viral, bacterial, or fungal infection of the lining of the brain and spinal cord, the meninges. The meninges are the three membranes that cover the brain and spinal cord.

Commonly used antibiotics to treat are—cotrimoxazole, erythromycin, penicillin and cefotaxime.

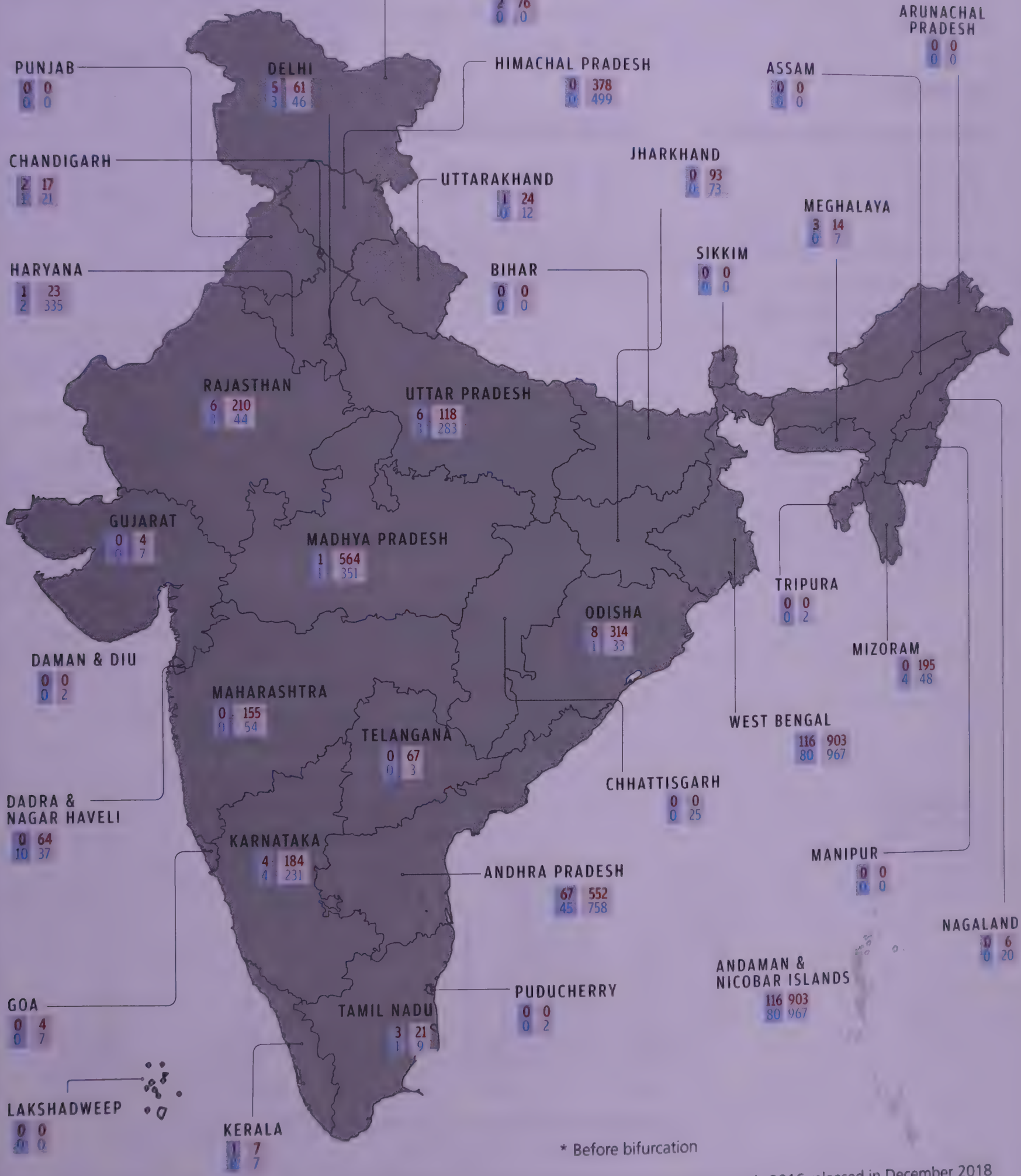
What is drug-resistant meningitis?

Resistance has been reported among *S pneumoniae* isolates against commonly used antibiotics such as cotrimoxazole, erythromycin, penicillin and cefotaxime.

SMALL DIP

India recorded 3 per cent decrease in meningococcal meningitis cases between 2017 and 2018

Deaths due to Meningococcal Meningitis
Cases due to Meningococcal Meningitis
XXX 2017 XXX 2018



* Before bifurcation

Source: National Health Profile 2018, 2019 and Global Burden of Disease Study 2016 released in December 2018

CRITICAL PATHOGEN

Escherichia coli is a fecal coliform bacteria commonly found in the intestines of animals and humans. WHO classifies it as a critical pathogen because of its high resistance to antibiotics

IN INDIA

RESISTANCE RECORDED

6

Aminoglycoside | Carbapenems | Cephalosporins (3rd gen) | Fluoroquinolones | Piperacillin-tazobactam | Polymyxin

DISEASES CAUSED

3

Urinary tract infections | Pneumonia | Diarrhoea

WHO priority pathogens

In 2017, WHO released the global priority pathogen list to align R&D with public health needs and support global coordination in the fight against AMR. The pathogens are grouped according to the species and the type of resistance

Priority 1: Critical

Acinetobacter baumannii; Pseudomonas aeruginosa; Enterobacteriaceae (*Klebsiella pneumoniae, Escherichia coli, Enterobacter* spp, *Serratia* spp, *Proteus* spp, and *Providencia* spp, *Morganella* spp)

Priority 2: High

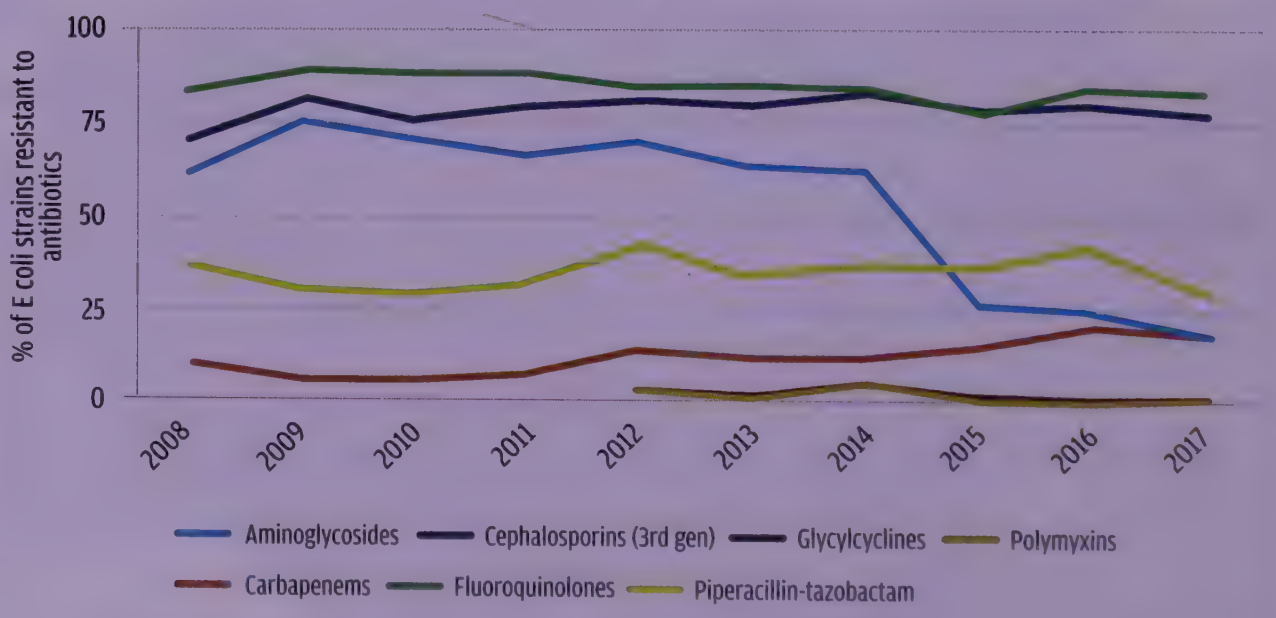
Enterococcus faecium, Staphylococcus aureus, Helicobacter pylori, Campylobacter, Salmonella spp, *Neisseria gonorrhoeae*

Priority 3: Medium

Streptococcus pneumoniae, Haemophilus influenzae, Shigella spp

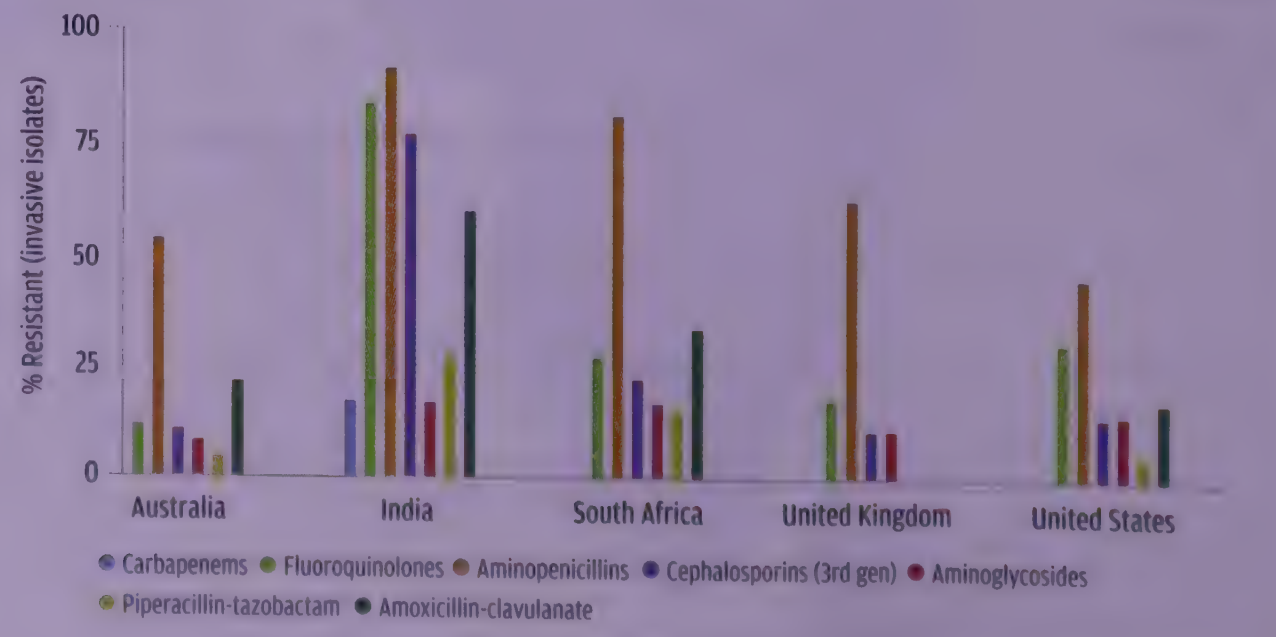
UNDER THREAT

Of the seven antibiotics that *E coli* has become resistant to, maximum resistance has been observed against fluoroquinolones (84 per cent of tested strains are resistant), followed by cephalosporins (77 per cent of tested strains are resistant)



A UNIQUE PROBLEM

India is the only country that has recorded *E coli* strains resistant to carbapenems



Source : Center for Disease Dynamics, Economics & Policy; As on November15, 2019

CRITICAL PATHOGEN

Acinetobacter baumannii is a gram-negative bacterium commonly found in immunocompromised individuals, particularly those who have experienced a prolonged (>90 days) hospital stay

IN INDIA

RESISTANCE RECORDED

8

Amikacin | Aminoglycosides | Ampicillin-sulbactam | Carbapenems | Ceftazidime | Fluoroquinolones | Glycylcycline | Polymyxins

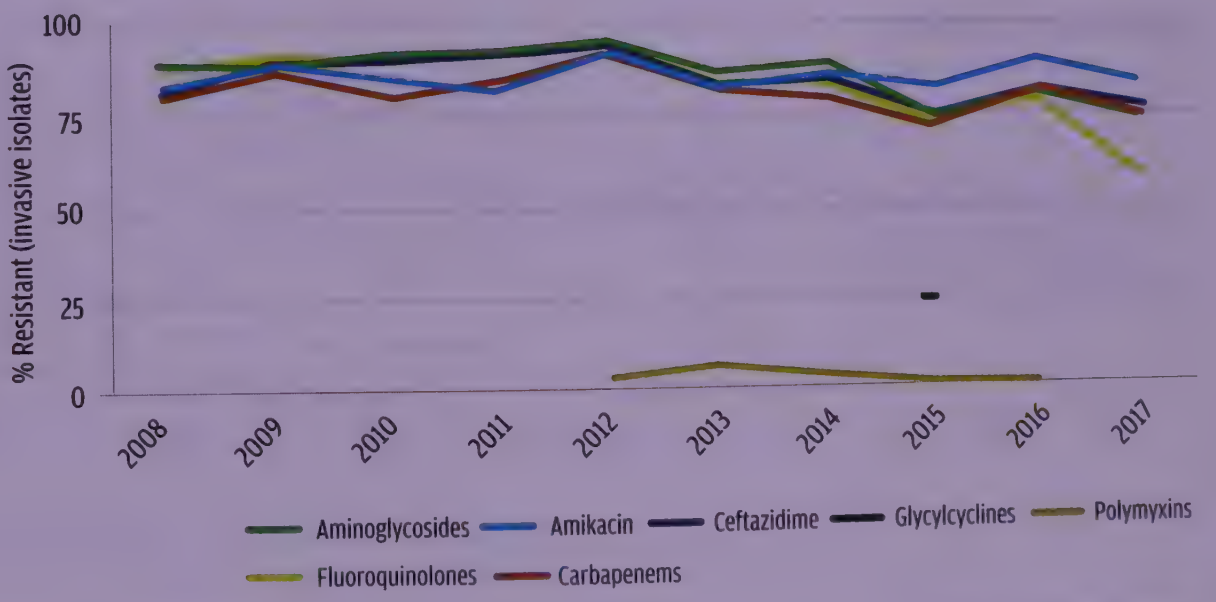
DISEASES CAUSED

4

Urinary tract infections | Pneumonia | Diarrhoea | Central nervous system infection

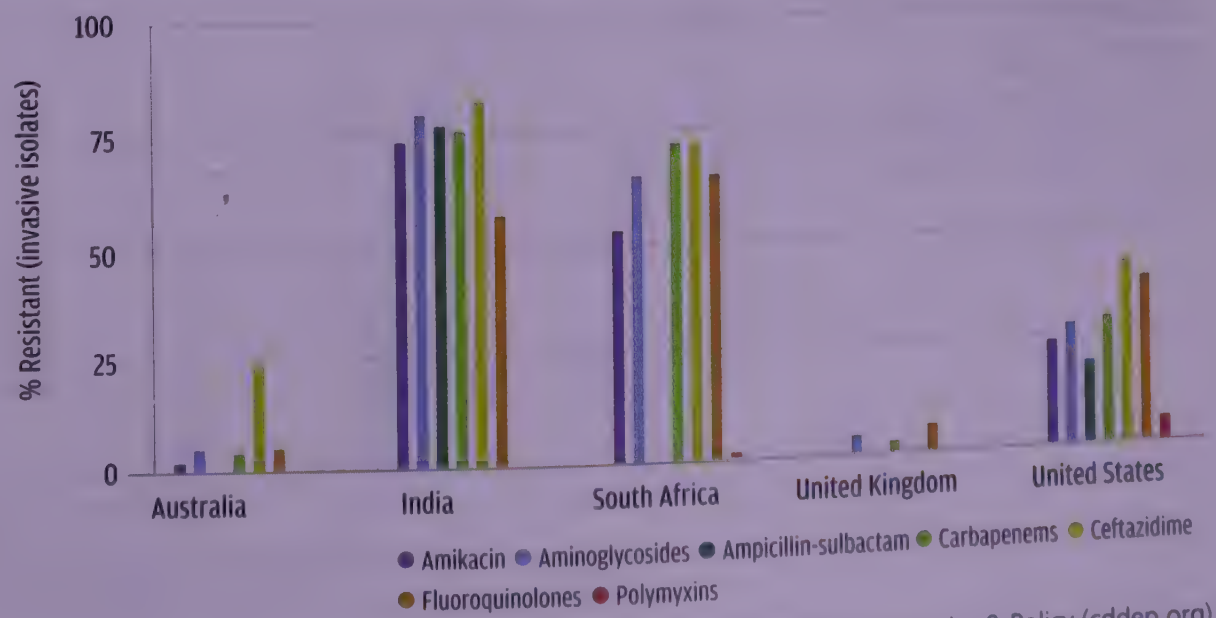
UNDER THREAT

Of the six antibiotics that *acinobacter baumannii* has become resistant to, maximum resistance has been observed against ceftazidime (84% of tested strains are resistant), followed by amikacin (75% of tested strains are resistant)



GLOBAL HOTSPOT

A baumannii strains in India exhibited resistance to six of the seven antibiotics



Source : Center for Disease Dynamics, Economics & Policy (cddep.org)

CRITICAL PATHOGEN

Enterococcus faecalis is a gram-positive bacterium found in the gastrointestinal tracts of humans and other mammals

IN INDIA

RESISTANCE RECORDED

6

Aminoglycosides (high-level) | Aminopenicillin | Fluoroquinolones | Linezolid | Vancomycin | Aminoglycosides

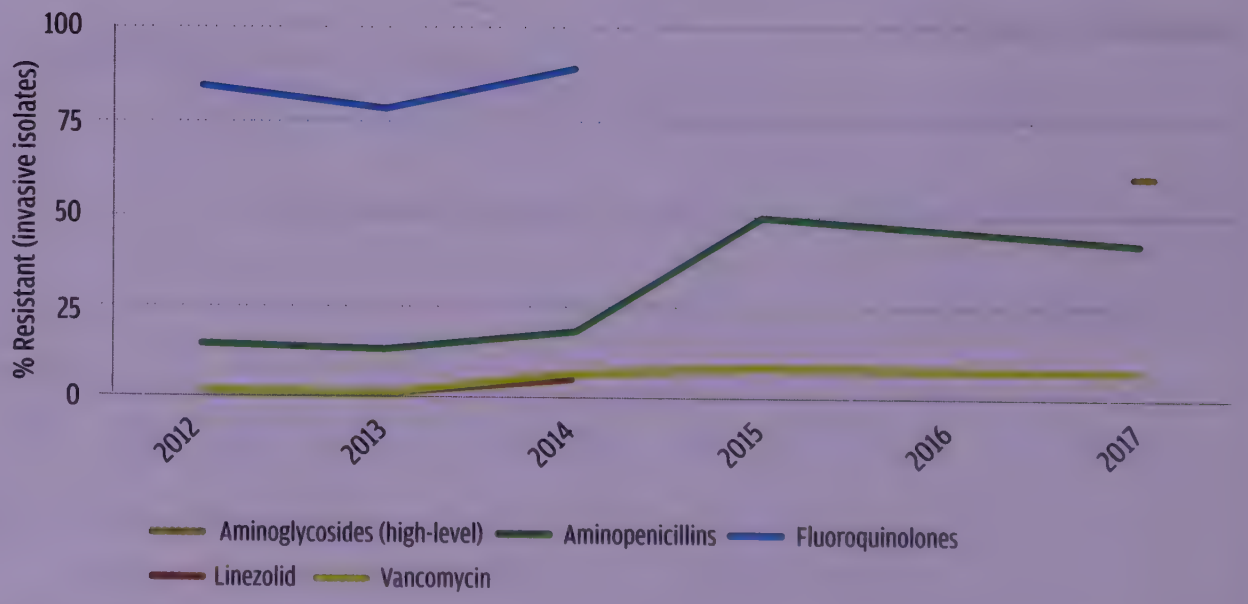
DISEASES CAUSED

3

Urinary tract infections | Endocarditis (an infection in the inner lining of the heart) | Wound infections

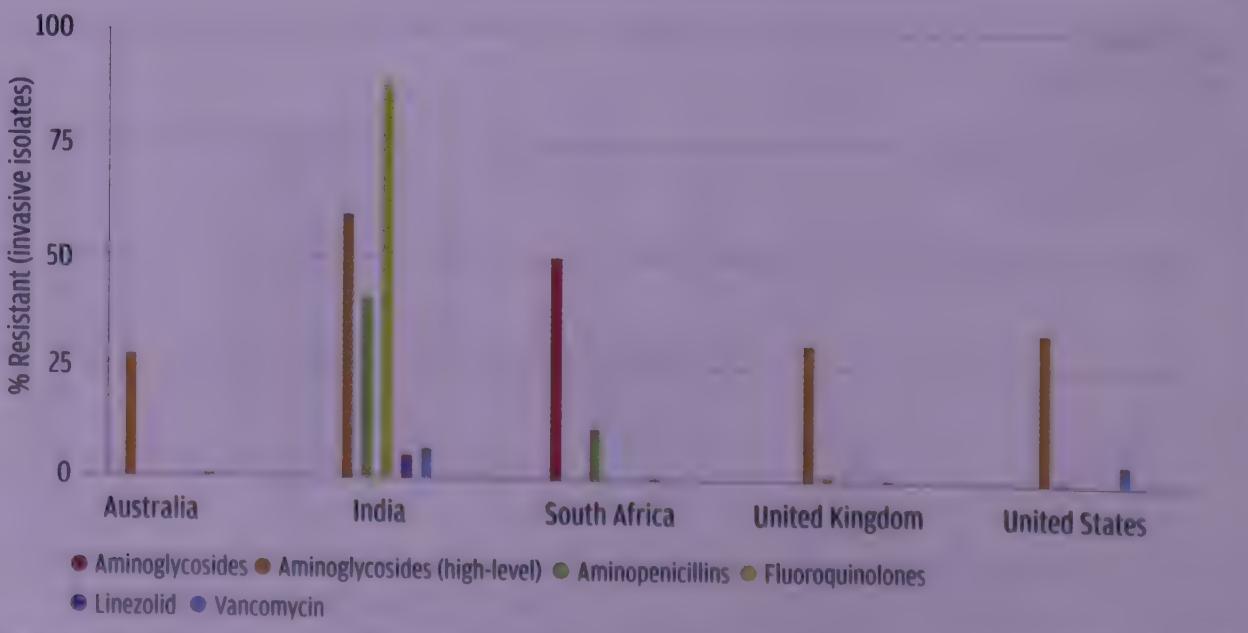
UNDER THREAT

Of the seven antibiotics that *Enterococcus faecalis* has become resistant to, maximum resistance has been observed against aminoglycosides (60% of tested strains are resistant), followed by aminopenicillin (41% of tested strains are resistant)



A UNIQUE PROBLEM

India is the only country that has recorded *E coli* strains resistant to fluoroquinolones and linezolid



Source Center for Disease Dynamics, Economics & Policy (cddep.org) Washington DC, Accessed on November 6, 2019

CRITICAL PATHOGEN

Pseudomonas aeruginosa is a gram-negative bacteria that is commonly found in soil, water and other moist locations. It usually affects persons with weak immune system

IN INDIA

RESISTANCE RECORDED

6

Amikacin | Aminoglycoside | Carbapenems | Cephalosporins (3rd gen) | Fluoroquinolones | Piperacillin-tazobactam

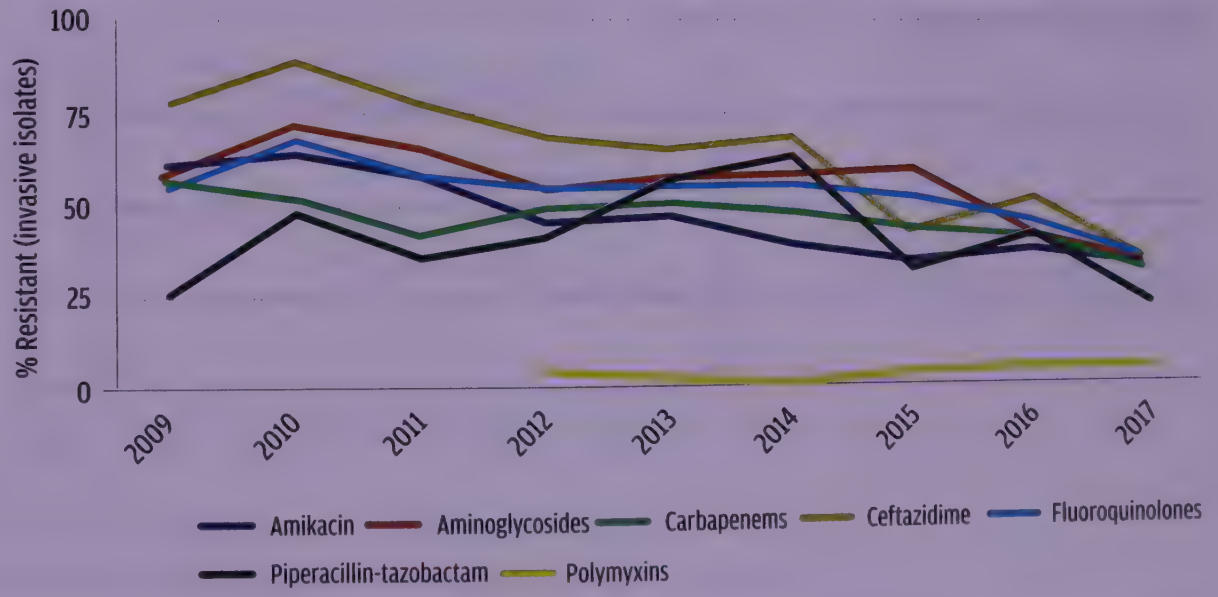
DISEASES CAUSED

7

Urinary tract infections | Respiratory system infections | Dermatitis | Soft tissue infections | Bacteremia | Bone and joint infections | Gastrointestinal infections

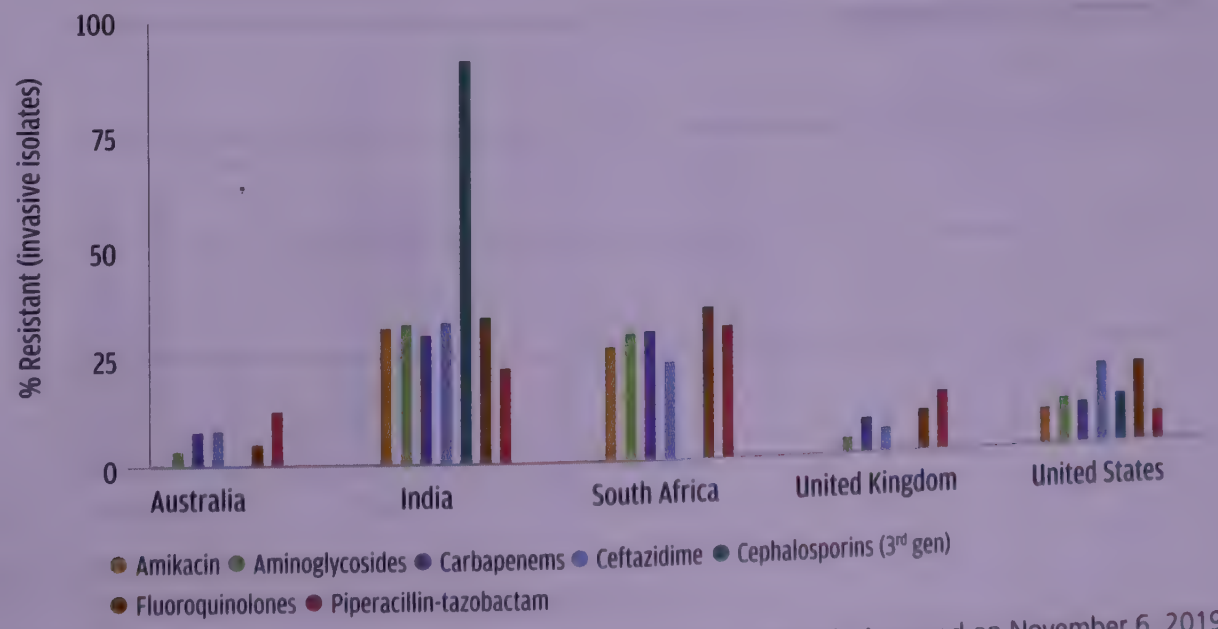
UNDER THREAT

Of the seven antibiotics that *Pseudomonas aeruginosa* has become resistant to, maximum resistance has been observed against fluoroquinolones (FQs) (34% of tested strains are resistant), followed by ceftazidime (33% of tested strains are resistant)



GLOBAL HOTSPOT

P aeruginosa strains in India recorded the highest resistance in five of the seven antibiotics



Source : Center for Disease Dynamics, Economics & Policy (cddep.org) Washington DC, Accessed on November 6, 2019

CRITICAL PATHOGEN

Klebsiella pneumoniae is a common gut bacteria that causes both invasive and non-invasive infections like meningitis, bacterial, pneumonia and conjunctivitis

IN INDIA

RESISTANCE RECORDED

8

Aminoglycosides | Amoxicillin-clavulanate | Carbapenems | Cephalosporins (3rd gen) | Fluoroquinolones | Piperacillin-tazobactam | Polymyxins | Glycylcyclines

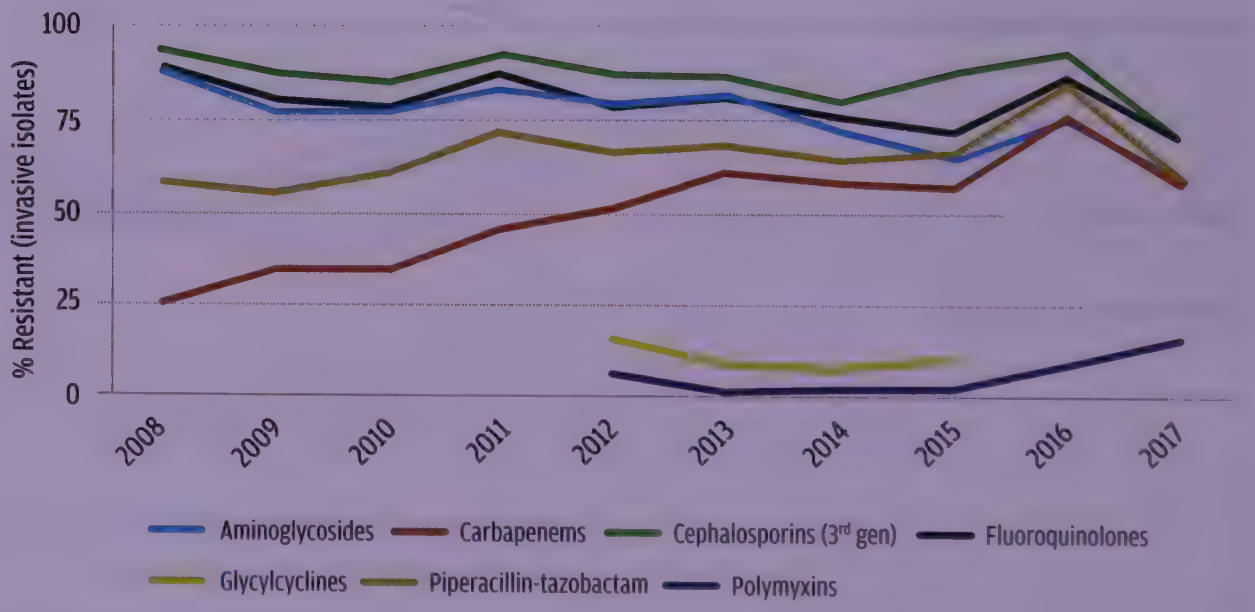
DISEASES CAUSED

4

Meningitis | Pneumonia | Bacteraemia | Conjunctivitis

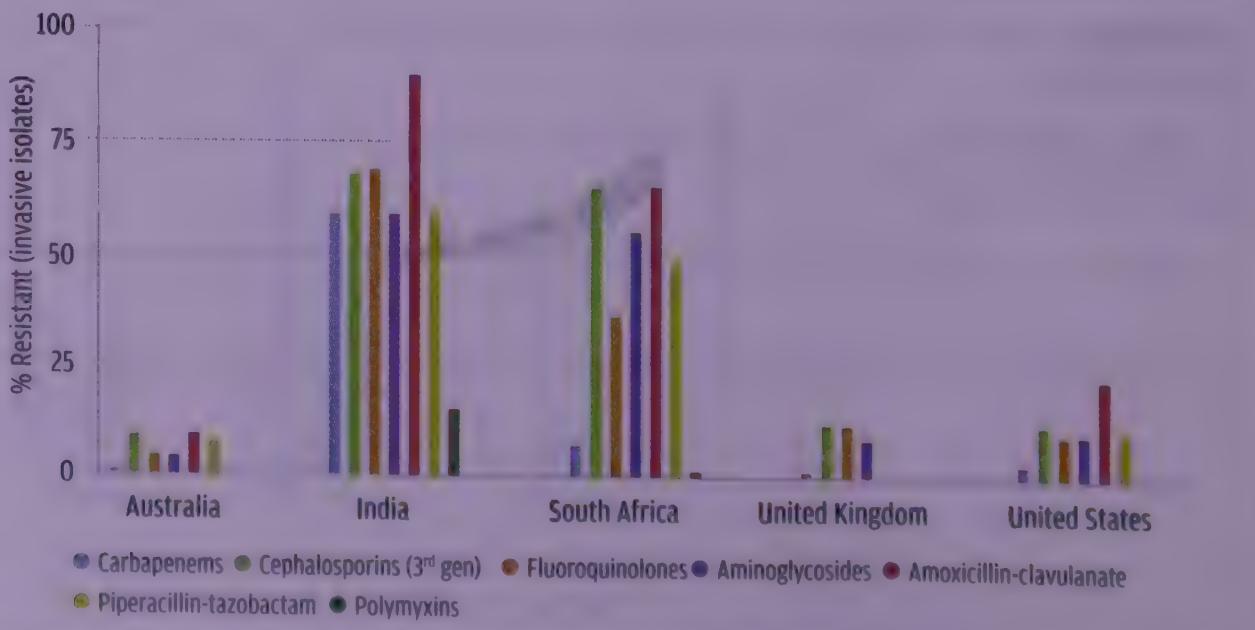
UNDER THREAT

Of the seven antibiotics that *Klebsiella pneumoniae* has become resistant to, maximum resistance has been observed against fluoroquinolones (FQs) (69% of tested strains are resistant), followed by piperacillin-tazobactam (59% of tested strains are resistant)



GLOBAL HOTSPOT

K pneumonia strains in India recorded the highest resistance in all of the seven antibiotics



Source : Center for Disease Dynamics, Economics & Policy (cddep.org) Washington DC, Accessed on November 6, 2019

CRITICAL PATHOGEN

Enterobacter aerogenes or *Klebsiella aerogenes* is a gram-negative pathogen generally found in the human gastrointestinal tract

IN INDIA

RESISTANCE RECORDED

8

Aminoglycosides | Amoxicillin-clavulanate | Carbapenems | Cephalosporins (3rd gen) | Fluoroquinolones | Piperacillin-tazobactam | Polymyxins | Glycylcyclines

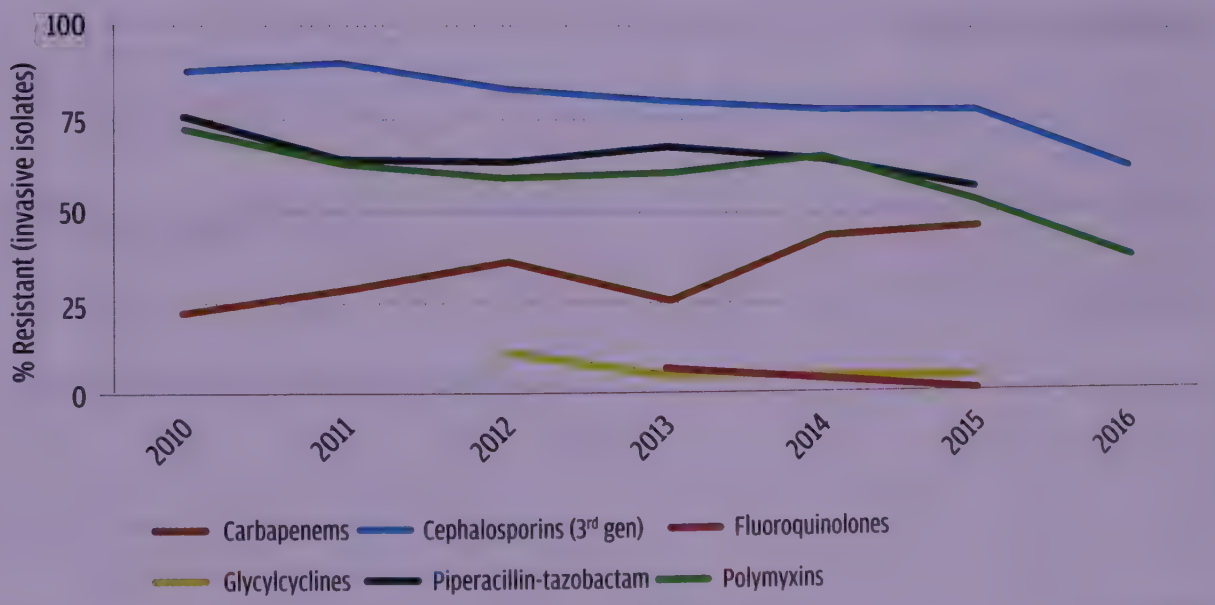
DISEASES CAUSED

5

Respiratory and Urinary tract infections | Osteomyelitis | Septic arthritis | Meningitis | Central nervous system infections

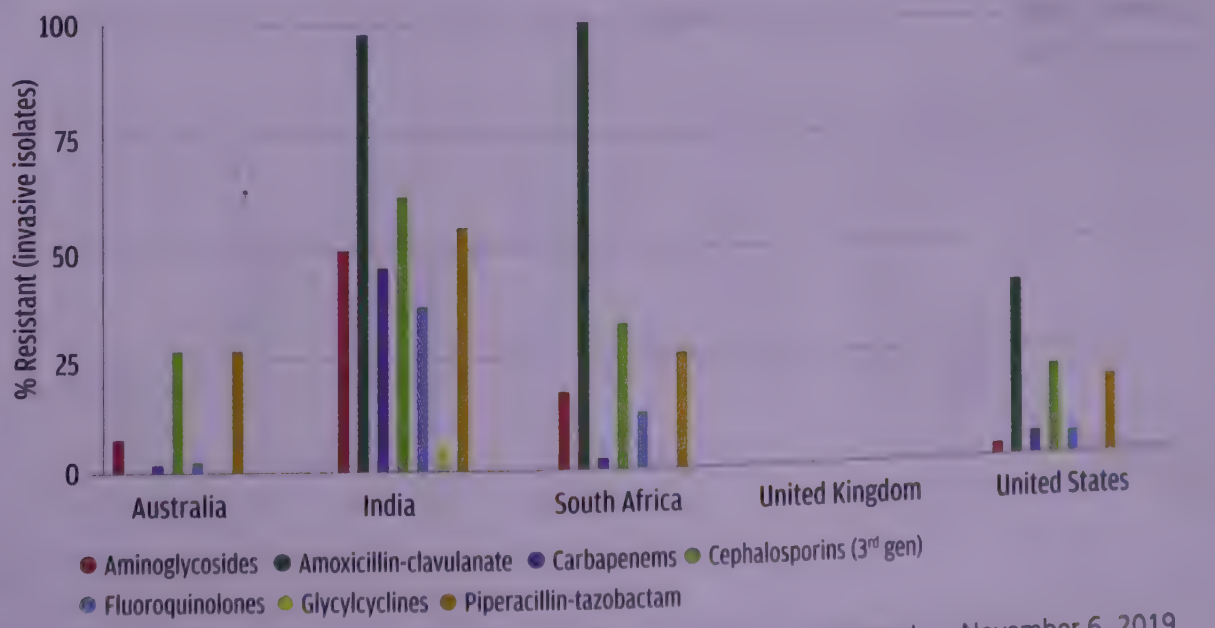
UNDER THREAT

Of the seven antibiotics that *Enterobacter aerogenes* has become resistant to, maximum resistance has been observed against cephalosporins (3rd gen) (62% of tested strains are resistant), followed by fluoroquinolones (FQs) (37% of tested strains are resistant)



GLOBAL HOTSPOT

E aerogenes strains in India recorded the highest resistance in six of the seven antibiotics



Source : Center for Disease Dynamics, Economics & Policy (cddep.org) Washington DC, Accessed on November 6, 2019

HIGH-PRIORITY PATHOGEN

Staphylococcus aureus is a major human pathogen that causes a wide range of clinical infections

IN INDIA

RESISTANCE RECORDED

9

Aminoglycosides | Aminopenicillins | Amoxicillin-clavulanate | Fluoroquinolones | Linezolid | Oxacillin (MRSA) | Rifampicin | Vancomycin | Macrolides

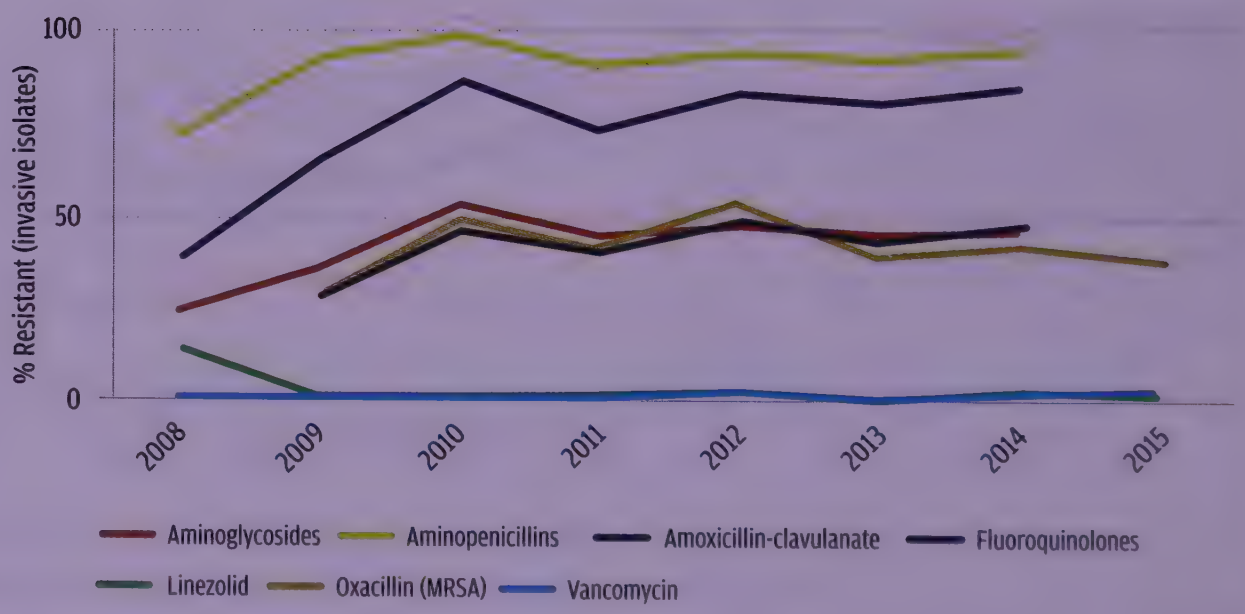
DISEASES CAUSED

4

Bacteremia | Infective endocarditis | Pneumonia | Bone infections

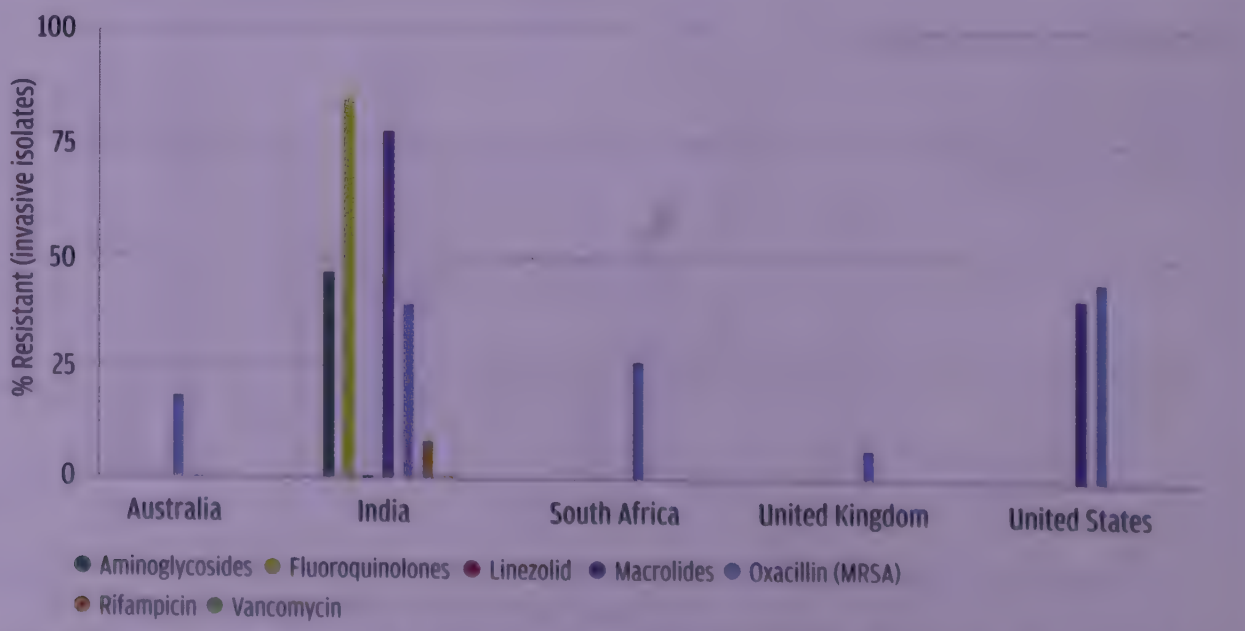
UNDER THREAT

Of the seven antibiotics that *Staphylococcus aureus* has become resistant, maximum resistance has been observed against oxacillin (MRSA) (62% of tested strains are resistant), followed by linezolid and vancomycin (1% of tested strains are resistant)



A UNIQUE PROBLEM

India is the only country that has recorded resistance of *S aureus* strains in all five antibiotics



Source : Center for Disease Dynamics, Economics & Policy (cddep.org) Washington DC, Accessed on November 6, 2019

MEDIUM-PRIORITY PATHOGEN

Streptococcus pneumonae is a major human pathogen responsible for pneumonia, meningitis and other serious infections

IN INDIA

RESISTANCE RECORDED

2

Macrolides | Penicillins

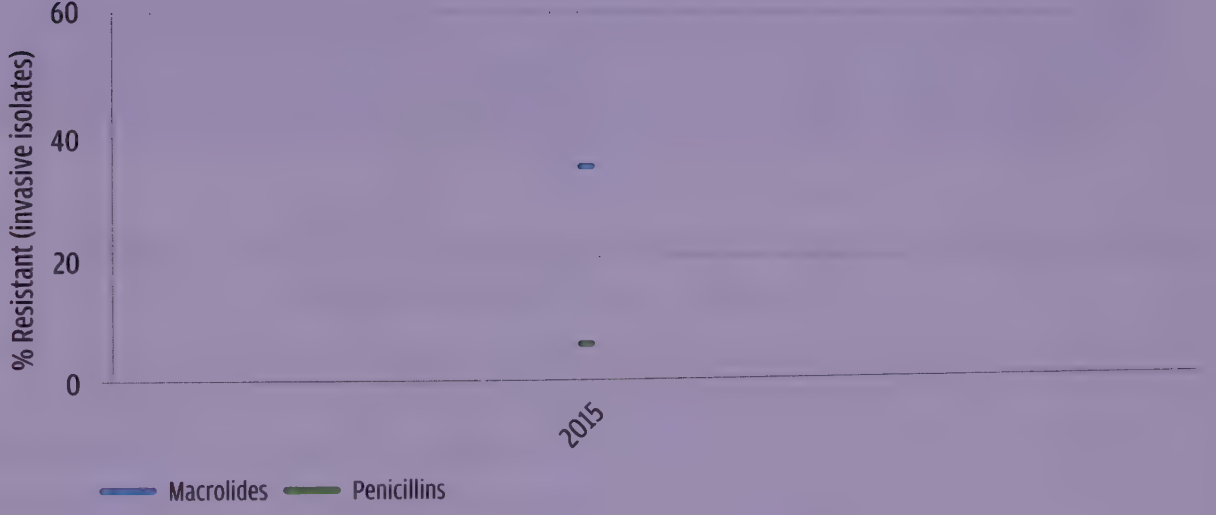
DISEASES CAUSED

4

Meningitis | Pneumonia | Bacteraemia | Conjunctivitis

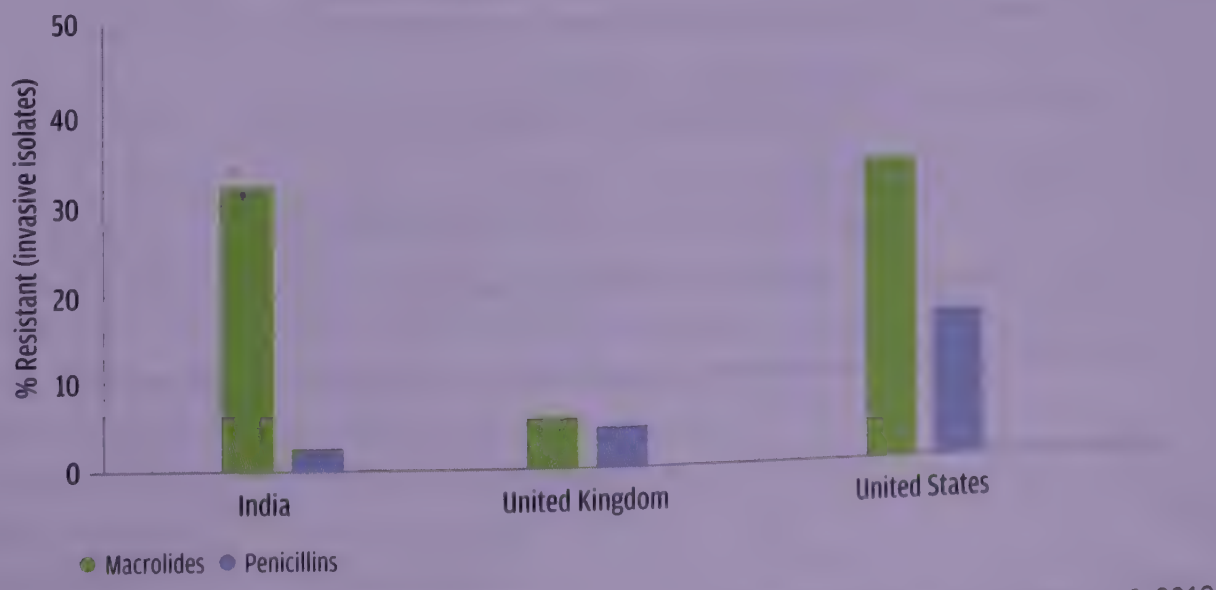
UNDER THREAT

Of the two antibiotics that *Streptococcus pneumonae* has become resistant to, maximum resistance has been observed against macrolides (32% of tested strains are resistant), followed by penicillin (3% of tested strains are resistant)



GLOBAL HOTSPOTS

US and India have recorded the highest number of antibiotics-resistant *S pneumonae* strains



Source : Center for Disease Dynamics, Economics & Policy (cddep.org) Washington DC, Accessed on November 6, 2019

LACK OF ACCESS

Shortage of first-line antibiotics, which are essential to treat a wide range of common infections, is a major public health threat

LEENA MENGHANEY, DUŠAN JASOVSKÝ, JYOTSNA SINGH

FRAGILE SUPPLY and shortages of first-line antibiotics—medicines used to prevent and treat a wide range of common bacterial infections—is a growing problem that is often neglected in deliberations on mitigation of antimicrobial resistance (AMR). Resistance to antibiotics has emerged as one of the biggest public health challenges of our times, threatening our ability to treat a number of infectious diseases and undoing much of the advances on healthcare made in the last few decades.

Increasingly, member states of the World Health Organization (WHO) and forums of governments such as the G20 are focusing attention on policies that encourage individual ministries of health to regulate overuse and irrational use of existing antibiotics and globally at research and development (R&D) of new antibiotics to treat resistant infections. However, access to antibiotics is often addressed as an afterthought.

WHO categorises the first-line, narrow spectrum drugs as "Access" group antibiotics, which should be widely available, affordable and quality-assured. It advocates that 60 per cent of the global consumption of all antibiotics should come from this category.

The other categories—"Watch" and "Reserve"—are recommended for specific, limited indications or for situations when all alternative antibiotics have failed. Any shortages or inconsistencies in the supply of first-line, narrow-spectrum "Access" antibiotics can adversely affect people who otherwise go untreated or are forced to use second- or third-line "Watch and Reserve" antibiotics. This is further fuelling drug resistance against them. It is a major barrier for people in the short-term, an obstacle to rational use, and, as such, an overlooked driver of antibiotic resistance. Without resolving shortages and supply instability, we cannot address AMR successfully.

As a humanitarian medical organisation, Médecins Sans Frontières (MSF) has documented recurrent shortages, inconsistencies in the supply chain, lack of appropriate formulations and insufficient suppliers for some "Access" group antibiotics—such as penicillins, gentamicin and co-trimoxazole—for its medical operations. Our supply division faces a multitude of challenges, including a lack of quality-assured sources and manufacturers enforcing minimum purchase order quantities that are difficult to meet.

Treatment of a broad range of bacterial infections—from sepsis and meningitis, toxoplasmosis, typhoid fever, to diphtheria, syphilis, pneumonia and others—is thus impacted. MSF is not alone in its experience. A lengthy and ongoing penicillin shortage is currently affecting several countries across the world, including India, where several of its health interventions including the programme to eliminate mother to child transmission of syphilis and to treat infants at risk of



congenital syphilis is facing a challenge with the availability and supply of penicillin. Other public health interventions are facing similar shortages of penicillin.

Health systems also face supply challenges. In Australia, the paediatric suspension of co-trimoxazole syrup has been out of stock for months, which has affected the treatment of a large number of aboriginal children with school sores. Similarly in India, the National AIDS Control Programme too has faced supply instability for co-trimoxazole syrup—an essential antibiotic—for opportunistic infections preventive therapy in infants and children with HIV. This is despite the fact that India is a major drug manufacturing country whose burden of infectious diseases is among the highest in the world.

A 2013 study from New Delhi exposed a sub-optimal availability of some "Access" group antibiotics, such as benzathine penicillin and amoxicillin, while other "Watch" and "Reserve" group antibiotics, such as fluoroquinolones and carbapenems, were freely available. A more recent *PLoS* study in India has documented the increasing consumption rates of last-resort antibiotics, such as carbapenems, lincosamides, glycopeptides, third-generation cephalosporins, linezolid and daptomycin, which belong to WHO's "Watch" and "Reserve" groups of antibiotics—thus, needlessly exposing patients and increasing the risk of drug-resistant bacteria to develop.

Such irrational use of antibiotics implies that "market failure" has set in. The pharmaceutical industry does not see profit in producing relatively inexpensive "Access" group antibiotics, while drugs that guarantee higher pay offs are ensured a reliable supply. Low margins—where sales are linked to the public sector and poor patients who have limited ability to pay—have prompted several producers in the domestic industry to discontinue manufacture and supply, rendering global access vulnerable. This, in turn, has sparked the exit of active pharmaceutical ingredients (API) manufacturers for some "Access" group antibiotics and the manufacturing of APIs for some antibiotics is thus,

becoming increasingly fragile.

Furthermore, if "Watch" and "Reserve" group antibiotics are promoted, marketed and prescribed over first-line treatment in the unregulated private sector, then demand for "Access" antibiotics will fall, further disrupting the market and increasing the likelihood of insufficient supply. A *The Lancet* study in 2017 confirmed that Indian domestic generic producers were predominantly selling irrational fixed dose combinations that contain "Watch" and "Reserve" group antibiotics, driving up sales of these categories rapidly by 73 per cent and 174 per cent respectively between 2007 and 2012.

India has a key role to play in not just improving the appropriate and ethical use of antibiotics, but also addressing the issues of shortages and supply instability of first-line "Access" group antibiotics. In this context, the recommendations of the UN Interagency Coordination Group (IACG) on Antimicrobial Resistance in a recent report that was submitted to the United Nations Secretary General are of particular importance for India. The IACG report advocates for improved forecasting, strengthening of procurement and supply chain management of antibiotics and the establishment of public or government-contracted production facilities to help mitigate shortages and ensure sustainable production and supply of antibiotics.

Indian generic producers continue to sell irrational fixed dose combinations that contain "Watch" and "Reserve" groups of antibiotics

India has a long history of public sector manufacturing in pharmaceuticals although a number of facilities are facing a state of neglect, struggling financially and have lost their capacity to produce, while others have been sold. However, some capacity still continues to exist. Karnataka Antibiotics & Pharmaceuticals Limited (KAPL)—a government enterprise—is a supplier of antibiotics such as penicillin to some health programmes. The Kerala state government's recent efforts, for example, to revive the Kerala State Drugs & Pharmaceuticals Limited could be crucial to secure supply of "Access" group antibiotics for the domestic market and public sector procurement by state governments. Other models such as Low Cost Standard Therapeutics—a not-for-profit trust and manufacturer of essential medicines not linked to unethical promotion and extraction of vast profit margins—also exist, and could produce "Access" group antibiotics.

Policies and mechanisms

Revival of public sector manufacturing alone will not address the crisis of instable supply and shortages of these essential antibiotics. It is unacceptable if an antibiotic needed to treat an infection is not available because we don't have a national system for coordinating and maintaining antibiotic supply. Mechanisms for collective data-sharing, improved forecasting and pooled procurement to meet the demand for "Access" group antibiotics among hospitals, public health programmes, central and state procurement agencies across the country are also needed.

Multiple examples of such regional and global pooled procurement mechanisms currently exist around the world, including the Global Drug Facility for TB that was set up to address the problem of antibiotic shortages and absence of quality-assured sources in the area of drug-resistant TB. Introducing a similar model in India for "Access" group antibiotics would not only reduce prices with manufacturers but also guarantee a more sustainable supply for treatment providers and access for patients. Policymakers need to secure a stable supply of all essential antibiotics and help save the lives of millions.


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Period.
Himalaya, in association with the United Sisters Foundation, is conducting menstrual hygiene awareness drives in the rural as well as urban slum pockets of Mumbai. Girls and women aged between 10 and 45 years are educated on **menstrual hygiene management** and **the use of eco-friendly alternatives like reusable cloth pads.**

SWELLING COST

The economic cost of antibiotic resistance in India is staggering; appropriate measures can trim it down

ASHOK J TAMHANKAR

IT MIGHT be better to hope that antibiotic resistance is only a misapprehension and not a reality, because antibiotic resistance is like a multi-headed hydra that needs to be tackled from multiple directions. If we want to avoid resistance development, we have to change our behaviour and practices in this context in multiple dimensions. If we fail to take the precautionary measures, antibiotic resistance will impact our life for long periods. When antibiotics do not work, the impacts are many—prolonged time taken for recovery from infections and illness, loss of work-days, loss of income and a likelihood of death. A report has predicted that by 2050, 10 million persons may die each year globally because of untreatable resistant infections if immediate measures are not taken to curb antibiotic resistance.

A standard unit of an antibiotic (SU) is the number of doses sold in a country; a dose being a pill or capsule or ampoule. In a recent research paper, the economic cost of antibiotic resistance in five priority pathogens of the World Health Organization (WHO) for various classes of antibiotics was estimated to be between US $0.1 and $0.6 per SU in the US, a high income country (HIC),. The same was between US $0.1 to $0.7 for Thailand, an upper-middle-income country (UMIC). As can be seen, between HIC and UMIC the Increase In range in economic cost is $ 0.1. India being a lower-middle-income Country (LMIC), let us assume the economic cost of antibiotic resistance associated with the consumption of 1 SU to increase by another $0.1, like it was between USA and Thailand and let us assume it to be between US $0.1-$0.8. Let us further assume the median of this to be US $0.45 i.e. about ₹32 for consumption of one SU of antibiotic for India considering all antibiotic classes together. (@ 1 US $= ₹70.5).

We have developed a statistical model (HISTI model) to estimate and predict 'human' antibiotic consumption in India. Based on the HISTI model and other relevant information from recent scientific literature, the current estimate of "human" antibiotic consumption for India would be about 20-22 billion SUs (population estimated as 1.35 billion). So the estimated economic cost due to antibiotic resistance for India (@ ₹32/SU) could be about ₹64,000–70,400 crore.

The actual figure may vary because of several factors, such as the actual consumption data, methods of calculation involved at various stages and conversion of SUs to defined daily doses (DDDs). Further, these cost calculations are based on resistance cost for five pathogens only and inclusion of other pathogens would increase the economic cost accordingly. There are some other issues also that need to be looked into for cost considerations. For example, in this calculation, we have not accounted for antibiotic consumption in the "non-human" sector, i.e. use in agriculture,

The antibiotic resistance holocaust has not yet hit us, but let us take appropriate measures and save ourselves. We need to remember that "A stitch in time saves nine"



poultry, aquaculture etc. The consumption in the non-human sector is generally at least about double of the human consumption and generates resistance within and outside the non-human sector, which can get transferred to human pathogens.

Residues in the environment

All the antibiotics consumed by humans and non-humans are not used up in the body and a large part of it is excreted, creating antibiotic residues in the environment. The excreta may also contain resistant bacteria. Further, there are huge amounts of antibiotic residues in effluents from antibiotic formulators, manufacturers, healthcare facilities that find their way into the environment. India is one of world's largest hubs for drug manufacturer and use. Appropriate wastewater/sewage carriage and treatment plants are non-existent in many places or when they exist, they do not completely remove antibiotics and pathogenic/ resistant bacteria from the wastewater. Exposure to antibiotic residues breeds resistance in bacteria. Thus, environment becomes a repository of antibiotic resistant bacteria that have the potential to transfer resistance to human pathogens.

Some socio-economic and behavioural factors typical to India also impact on antibiotic consumption, resistance levels and economic burden. For example, non-allopathic (AYUSH+ informal, untrained quacks) healthcare personnel, over/under prescribing of antibiotics, poor sanitation, population below economic threshold level, crowding of people/ animals, non-availability of clean drinking water, poor animal husbandry, poor hygiene and poor governance (corruption). All these spread the contagion. It is difficult to account for economic costs for them.

Economic costs could be measured based on resistance too. But hopefully, measuring the economic costs based on antibiotic consumption, as we have done here, takes into account the impact of all the other sectors automatically, if we consider

a simple paradigm: "The more the impact of non-human, environmental and socio-economic-behavioural factors, the more will be the infections, leading to more antibiotic consumption, which would lead to more resistance and further more antibiotic consumption."

However, if it is not so simple and if this paradigm is not applicable, we can take the estimated compounded economic costs to India, considering a one-fold enhancement due to each sector, to be between ₹128,000 and ₹140,800 crore after contribution of the non-human sector, ₹192,000-₹211,200 crore after further contribution from the environmental sector and ₹256,000-₹282,000 crore after further contribution due to the socioeconomic-behavioural factors. As time passes and the problem of resistance increases, the paradigm will not remain simple as considered here and the economic cost could turn into multiples of the current estimates.

India's economic cost due to antibiotic resistance and increased consumption of antibiotics is ₹256,000-282,000 crore

Reducing resistance cost

If we want to curb the antibiotic resistance before it takes uncontrollable proportions and compounds India`s economic losses, we must understand the important drivers for incidence of diseases, use of antibiotics and antibiotic resistance in India and find out how we can curb them. Let us understand that behaviour modification is an overarching factor involved in beneficially managing all the other factors. We have to understand that we cannot change easily individual or societal behaviour (human or non-human), we can only facilitate for the change of behaviour.

A major adverse factor in India is infection generation due to general unclean environment and the lack of infection prevention and control in healthcare facilities. Both are socio-behavioural issues with economic factors ingrained in them and require political will to tackle them. The former is being addressed by Prime Minister Narendra Modi himself by taking initiatives such as Swachh Bharat Mission (inclusive of toilet construction), cleaning up of waterways (e.g. rivers like the Ganga). Just to understand the magnanimity of proportions, the projected cost of 100 million toilets in rural India is `1.96 lakh crore or US$28 billion. A WHO report informs that for every US $1 invested in sanitation, there was a return of US $5.50 in lower health costs, more productivity and fewer premature deaths. Thus, sanitation initiatives should pay back towards reducing resistance-related economic costs.

As far as healthcare facilities are concerned, the minimum we can do is to ensure provision of soap and water (alcohol-based hand rub where possible) for hand hygiene, disinfectants for environmental (floor/ surface) hygiene and continuous training and reminders in this context. A study has found the cost-benefit ratio for hand hygiene to be 13.4 in the context of one organism alone (Methicillin-resistant *Staphylococcus aureus*).Thus, investment in these aspects will cut the root of infection generation itself, resulting in less consumption of antibiotics, reduced problem of resistance and consequently less economic losses.

Restricting antibiotic use in food-producing animals has been found to reduce resistance up to 39 per cent in animals and 24 per cent in humans. The Union government has already formulated action plans to reduce unwarranted use in the non-human sector, which indicates that the economic cost for resistance on this account should reduce significantly in India.

In the environmental sector—for effluents from pharmaceutical industry, healthcare facilities, animal-agri-aquaculture sector and even human settlement (housing colonies) sector, India should adopt a "nip in the bud" policy—meaning stopping environmental

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contamination by antibiotics and pathogenic/ resistant bacteria at the origin itself. For this, instead of waiting for designing, planning, sanctioning of huge treatment plants, which can take years, the policy should be the use of decentralized, resource efficient, "on-site treatment plants with zero release (complete neutralisation) of antibiotics and resistant bacteria (OnSTreP-ZARB)" using sunlight/ visible light and innovative relatively inexpensive technologies.

The planning and execution for small onsite treatment plants does not need huge funds and can be started immediately. Their use could be modular in nature and numbers should be increased, not the size. These will generate manufacture and repair jobs in the small-scale sector and thus the payback for resistance reduction and resistance cost reduction will start immediately.

"One Health" approach is a concept wherein human, non-human and environment sectors are tackled together from the perspective of reducing antibiotic resistance. Thus, instead of making efforts to reduce resistance sector wise, a comprehensive programme is undertaken with the involvement of all the sectors. As is obvious, a "One Health" approach will reduce resistance cost appreciably.

"One Health" is when human, non-human and environment sectors are tackled together to reduce antibiotic resistance

The involvement of AYUSH professionals and paramedics is important in personnel deficient India to provide abundant healthcare. Untrained informal providers (quacks) also fill an important void and cannot be wished away. They should be given constant and continued training on antibiotic resistance and ways of reducing it. The same holds true for allopathic practitioners too. Last but not the least is conducting antibiotic resistance awareness campaigns aimed at all the stakeholders through various audio-visual mediums like community radio, TV, posters and personalised lectures. A campaign event with an interactive lecture can cost as low as ₹100 and is very effective. The government and people in low and middle income countries should use this effective method, which really delivers the message at a low cost.

Some basic tenets can have an enduring impact on reducing the economic cost of antibiotic resistance as well as reducing the antibiotic resistance burden itself. An investment in the following will have payback for the economy. These tenets are:

- Continuance and enhancement of Swachh Bharat Mission including waterway cleaning;
- Hand hygiene and clean environment at healthcare facilities;
- Restricting antibiotic use in food-producing animals;
- Restricting environmental contamination by decentralised "On-Site Treatment Plants with Zero release (complete neutralisation) of antibiotics and resistant bacteria (OnSTreP-ZARB)" at contamination generating effluent sources;
- Taking up a "One Health" approach;
- Continued training of allopathic, AYUSH and informal (quacks) healthcare providers in antibiotic context; and,
- Repeated "Antibiotic Resistance Awareness Campaigns" aimed at all stakeholders, particularly the general public.

TRANSMISSION FACTOR

The environmental dimension of antimicrobial resistance

AMIT KHURANA, RAJESHWARI SINHA



ANTIMICROBIAL RESISTANCE (AMR) is a complex global public health threat. Antibiotics are becoming ineffective against common infectious diseases which were easily treated earlier. Rising AMR poses a grave threat to the gains made by modern medicine. AMR in the environment is accelerated by the presence of antibiotic resistant bacteria, antibiotic resistance genes (ARGs) or antibiotic residues, which collectively could be termed as AMR determinants. A continuous and perhaps ever-lasting interplay among the determinants has set the ground for a scenario similar to a chain reaction, which is difficult to stop. Until recently, AMR containment in the environment and in waste was a neglected agenda. It was only in 2015 that the World Health Organization (WHO) came out with the Global Action Plan on AMR, which provides limited guidance on the environment. While global deliberations on environmental dimensions of AMR have now begun, the specifics around the issue are missing. For example, there is limited guidance on environmental AMR surveillance such as the one on food-producing animals in WHO's *Integrated Surveillance of Antimicrobial Resistance in Foodborne Bacteria*. Similarly, WHO guidelines on the use of medically important antimicrobials in food-producing animals also suggest progress of global guidance in the animal sector.

This limited action on the environment is disappointing, but not surprising, as managing the environment is not the key mandate of WHO, the Food and Agriculture Organization of the United Nations (FAO) and the World Organisation for Animal Health (OIE), the three major stakeholders in the fight against antibiotics. In WHO's action plan, the human side of the AMR crisis received attention, but largely ignored other sources such as AMR in the environment. In 2017, the United Nations Environment Programme (UNEP) was roped-in to fill this missing gap. But due to the long delay in initiating action, a concrete set of guidelines for policymakers and stakeholders is still a distant reality.

In 2016, the food safety and toxins team at the Centre for Science and Environment (CSE), a New Delhi based non-profit, assessed the National Action Plans (NAPs) of 18 countries to analyse their focus on the environmental aspects of AMR. The assessment, which mostly comprised action plans of developed countries, revealed inadequate attention on the environment, compared to human health and the animal sector. In case of the environment, the NAPs talked largely about the need for greater research to understand AMR in the environment. It is only in the last few years that countries—which recently developed new action plans or revised their earlier versions—have outlined their approach to address AMR determinants in the environment. This is encouraging and reflects the willingness of a country to own up role in perpetuating the problem. But in the absence of comprehensive global guidelines, there is inadequate action on the ground. This would be detrimental in addressing AMR, which has become a global phenomenon and is spreading due to travel of people, animals and food.

75-90

per cent of antibiotics consumed by animals are excreted through fecal matter

The impact of limited global guidance will further reflect at the national level, wherein the environment and waste management efforts have historically focused on pesticides and heavy metals, and understanding the intricacies of microbiology is poor. The need of the hour is to generate momentum in the environmental dimensions of AMR at the global level as well as coordinated country-level advocacy programmes to make environmental stakeholders aware and secure their buy-in and commitment.

ENVIRONMENT ON RADAR

Focus on environment in India's National and State Action Plan on AMR

India's NAP put a strong focus on adopting a harmonized approach to addressing AMR in multiple sectors, including the environment. The plan stresses on surveillance, bio-security and waste management to reduce the impact of AMR in the environment. The Delhi Declaration on AMR, released with the plan, also reflected the inter-ministerial consensus to contain AMR. It was jointly endorsed by 12 ministries, including the Ministry of Environment, Forest and Climate Change (MoEFCC). Following the NAP, State Action Plans (SAPs) of Kerala and Madhya Pradesh have also stressed on the need for effective surveillance in environment and waste management. The committee working on Delhi AMR, which is on its way to develop its SAP, is also focusing on tackling environmental spread of AMR due to improper drug disposal or inadequate waste management from hospital settings, sewage treatment plants etc. While the plans look good, it is time, these are effectively implemented. CSE had played a key role in placing environment at the forefront while development of India's national and state action plans

Mounting evidence

CSE has been working to address the environmental aspects of AMR through policy research, field research and advocacy to push for necessary changes for containment of AMR in the environment. Some of CSE's studies on AMR in the environment show the magnitude of problem in the country.

AQUACULTURE ENVIRONMENT: In 2016, CSE analysed the waste management practices of aquaculture farms using antibiotics. CSE researchers visited intensive and semi-intensive aquaculture farms across six districts in West Bengal—the second highest fish producing state in the country. These included 22 farms, including six hatcheries across districts of North 24 Parganas, South 24 Parganas, Purba Medinipur, Bardhaman, Nadia and Hooghly.

Aquaculture waste is largely liquid. It also contains unconsumed fish feed, dead fish, plankton, faecal matter, egg shells, and chemicals, including antibiotics. CSE found that across farms and hatcheries, there was no system to treat wastewater, and untreated wastewater was being discharged into canals as a common practice. Water from these canals is sourced downstream and reused in brood-stock ponds or released into agricultural fields. Solid waste, including unused and expired antibiotics, was often being disposed by burying in pits. All this could facilitate the passage of residual un-metabolised antibiotics, antibiotic resistant bacteria or ARGs from aquaculture farms into the larger environment.

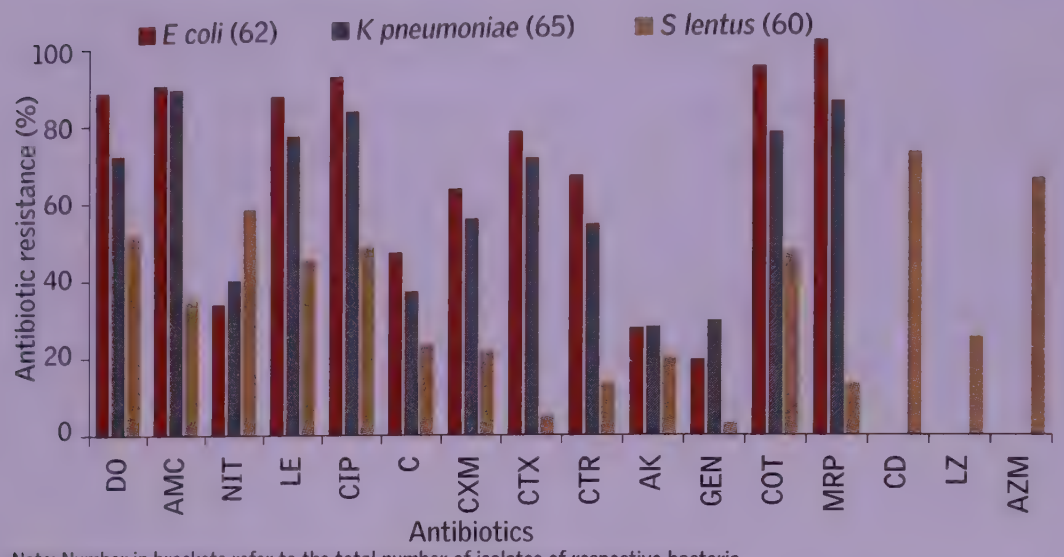
While the Coastal Aquaculture Authority (CAA) guidelines addresses waste management in brackish water farms, its implementation was found to be an issue. Almost none of the farms or hatcheries had effluent treatment systems (ETS). Big farmers were unwilling to bear the high cost of setting up an ETS, whereas medium to small farmers were either unaware or preferred utilising the designated ETS area for fish farming instead.

AMR surveillance and environmental standards are crucial and should be part of National Action Plans of countries. A failure to incorporate these would limit addressing AMR through the One Health approach

What CSE's study says

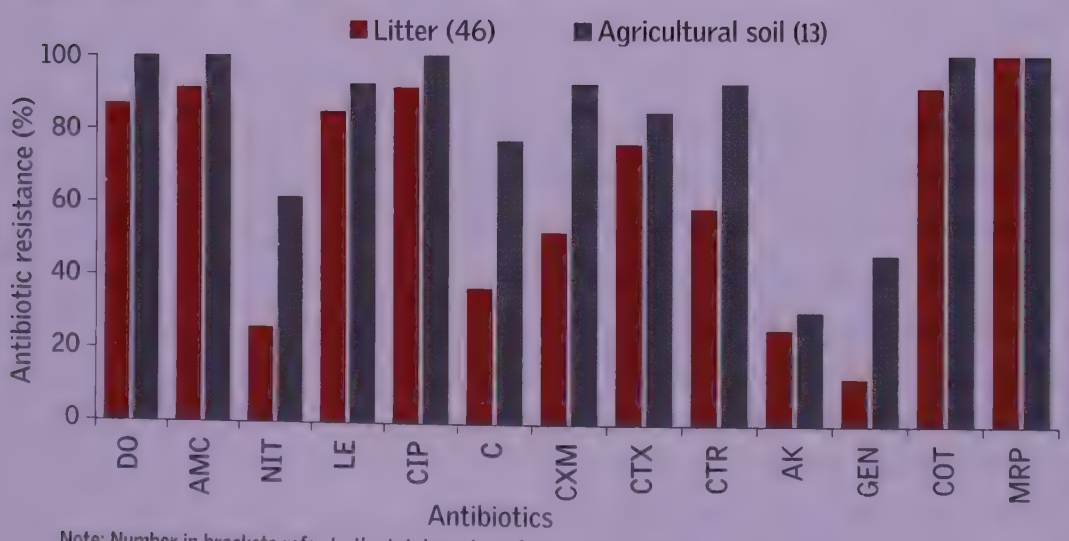
Conducted in 2017 in samples collected from four states

Antibiotic resistance in poultry farm environment



Note: Number in brackets refer to the total number of isolates of respective bacteria

Antibiotic resistance in *E coli* from litter and agricultural soil samples



Note: Number in brackets refer to the total number of isolates of *E coli*

Antibiotics or antibiotics against which the resistence tested | DO = Doxycycline Hydrochloride; AMC = Amoxyclav; NIT = Nitrofurantoin; LE = Levofloxacin; CIP = Ciprofloxacin; C = Chloramphenicol; CXM = Cefuroxime; CTX = Cefotaxime; CTR = Ceftriaxone; AK = Amikacin; GEN = Gentamicin; COT = Co-trimoxazole; MRP = Meropenem; CD = Clindamycin; LZ = Linezolid; AZM = Azithromycin

There was also no supervision or monitoring by the authorities concerned. The CAA guidelines indicate mandatory registration of shrimp farms, and setting up of an ETS is a pre-requisite. But this is not followed in practice and most farmers simply do not register their farms. Small farmers are not interested in registration, and big farmers manage to side-step such requirements by influencing higher authorities.

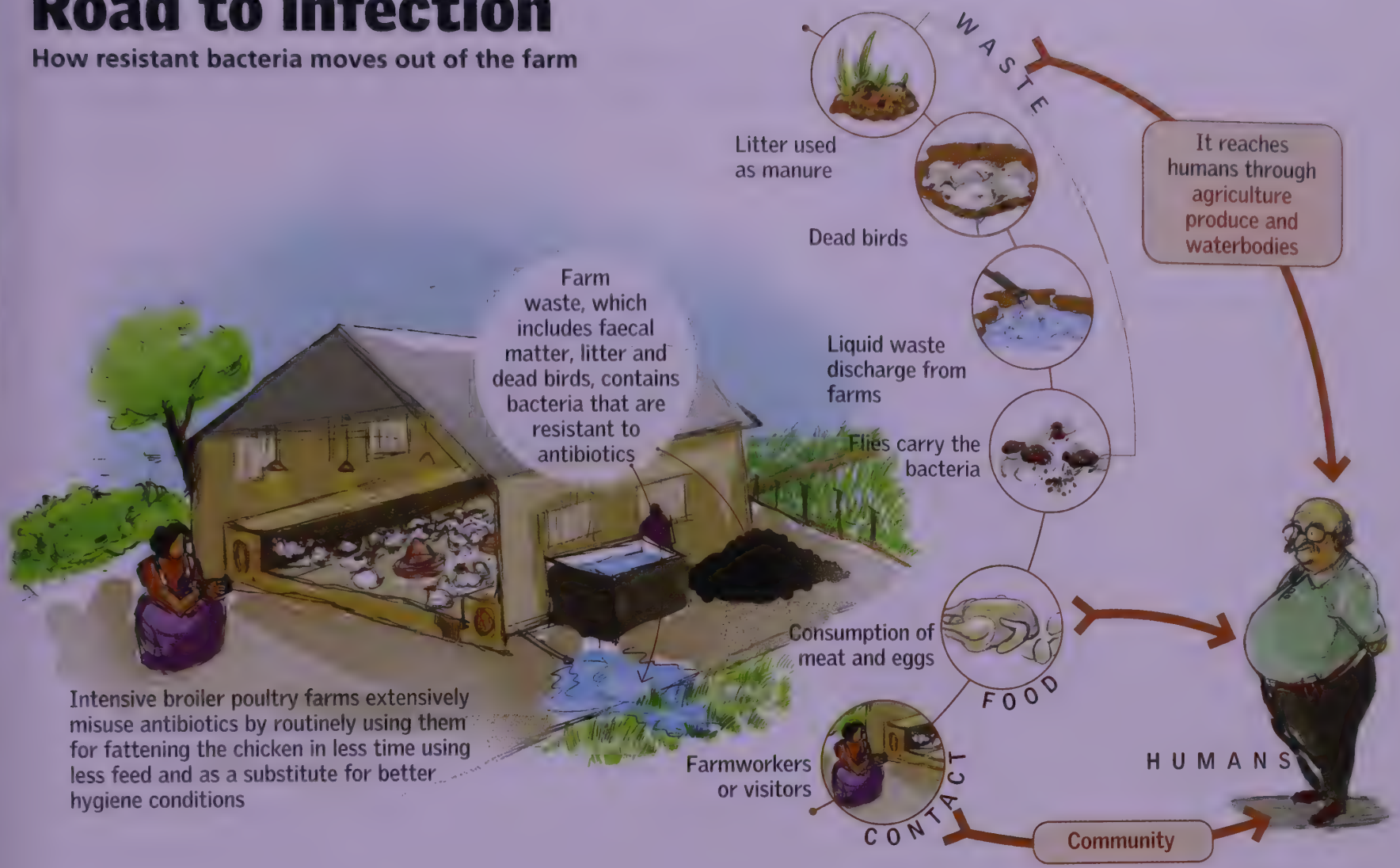
POULTRY ENVIRONMENT: In 2017, CSE conducted a study to understand the extent of antibiotic resistance in the broiler poultry environment and the spread of resistant bacteria from poultry farms to the environment. The study covered broiler farms in four key poultry meat-producing states—Uttar Pradesh, Rajasthan, Haryana and Punjab—which collectively contributed about 40 per cent of total poultry meat production in India.

Three bacteria—*Escherichia coli (E coli)*, *Klebsiella pneumoniae (K pneumoniae)* and *Staphylococcus lentus (S lentus)*—were isolated and identified from the samples collected by CSE. *E coli* and *K pneumoniae* strains cause meningitis, urinary tract infections and respiratory illnesses such as pneumonia. Patients with low immunity too are also at high risk of contracting *K pneumoniae* infections. The isolated bacteria were tested individually against antibiotics selected on the basis of their extent of use in poultry and importance to humans. Ten of the antibiotics belong to WHO's critically important class for human medicine.

The study found alarmingly high levels of drug resistance not just in the bacteria isolated from the chicken litter, but also from the soil samples collected from the poultry farm as well as in the neighbouring agricultural land. All the *E coli* isolates tested were found to be multi-drug resistant, which means they were resistant to at least three antibiotic classes. One in every six *E coli* isolates was resistant to 12 of the 13 tested antibiotics. Among the three bacteria, highest resistance was found in *E coli* (*see* "What CSE's study says"). Similar high resistance pattern was also observed in case of *K pneumoniae*. The study not only established that poultry farms are reservoirs of antibiotic resistant bacteria, but also showed that resistance

Road to infection

How resistant bacteria moves out of the farm



is moving out of the farms to neighbouring areas. The study found a similar proportion and similar resistance pattern in the *E coli* isolates collected from poultry litter and agricultural soil where the untreated litter was used as manure. There was also a strong statistical correlation between the resistance pattern in the isolates in poultry litter and agricultural soil.

PHARMACEUTICAL AND INDUSTRIAL ENVIRONMENT: In 2017, CSE investigated the waste management practices of pharmaceutical manufacturing units in the Baddi-Barotiwala-Nalagarh industrial area in Himachal Pradesh, which is one of India's largest pharmaceutical manufacturing hubs. The hub hosts around 500 small, medium and large pharmaceutical manufacturing units, some of which manufacture antibiotic active pharmaceutical ingredients or even use them to make antibiotic formulations.

CSE found that improper methods of waste disposal were being practiced. In many cases, effluents were discharged through outlets behind the manufacturing plant into bushy areas. The released effluent accumulated in, or flowed through *nallahs*, canals and rivulets into the nearby Sirsa river.

Manufacturers were also injecting effluents into bore wells at night. To cut costs, they were not transferring solid waste to the treatment, storage and disposal facilities. Instead, solid waste was handed over to scrap dealers or dumped in open areas and burnt. Some large companies claimed their plants to be Zero Liquid Discharge (ZLD), which means that wastewater is vapourised and the residual concentrate is incinerated so that no wastewater leaves the plant. However, to save on operational expenses, not all of them would operate 24x7

throughout the year. Moreover, setting up a ZLD plant requires very high investment, which is not affordable to medium or small scale manufacturers. Small-scale industries generally used primary or secondary effluent treatment plants (ETPs), which were conventionally not designed to remove residual antibiotics from the effluents. The common effluent treatment plant (CETP) in Baddi, which receives effluents from all these industrial units, was found to be working only at a partial capacity.

Many industries did not send their effluents to minimise the cost of CETP membership fees. In other industries, sewer lines were not properly connected to the CETP and opened directly into the Sirsa river. The study revealed how improper waste disposal has paved the way for the entry of residual antibiotics from pharmaceutical manufacturing waste into the environment and contributed to the spread of AMR.

Structuring environmental AMR

In view of AMR, the environment can therefore be structured into point and non-point sources of pollution. The point sources that are of concern w.r.t. AMR could be segregated into factories, healthcare settings, farms and household/community settings (See "Structure of the environment"). AMR determinants in solid or liquid waste from these sources may directly or after treatment, reach the larger environment such as soil and water.

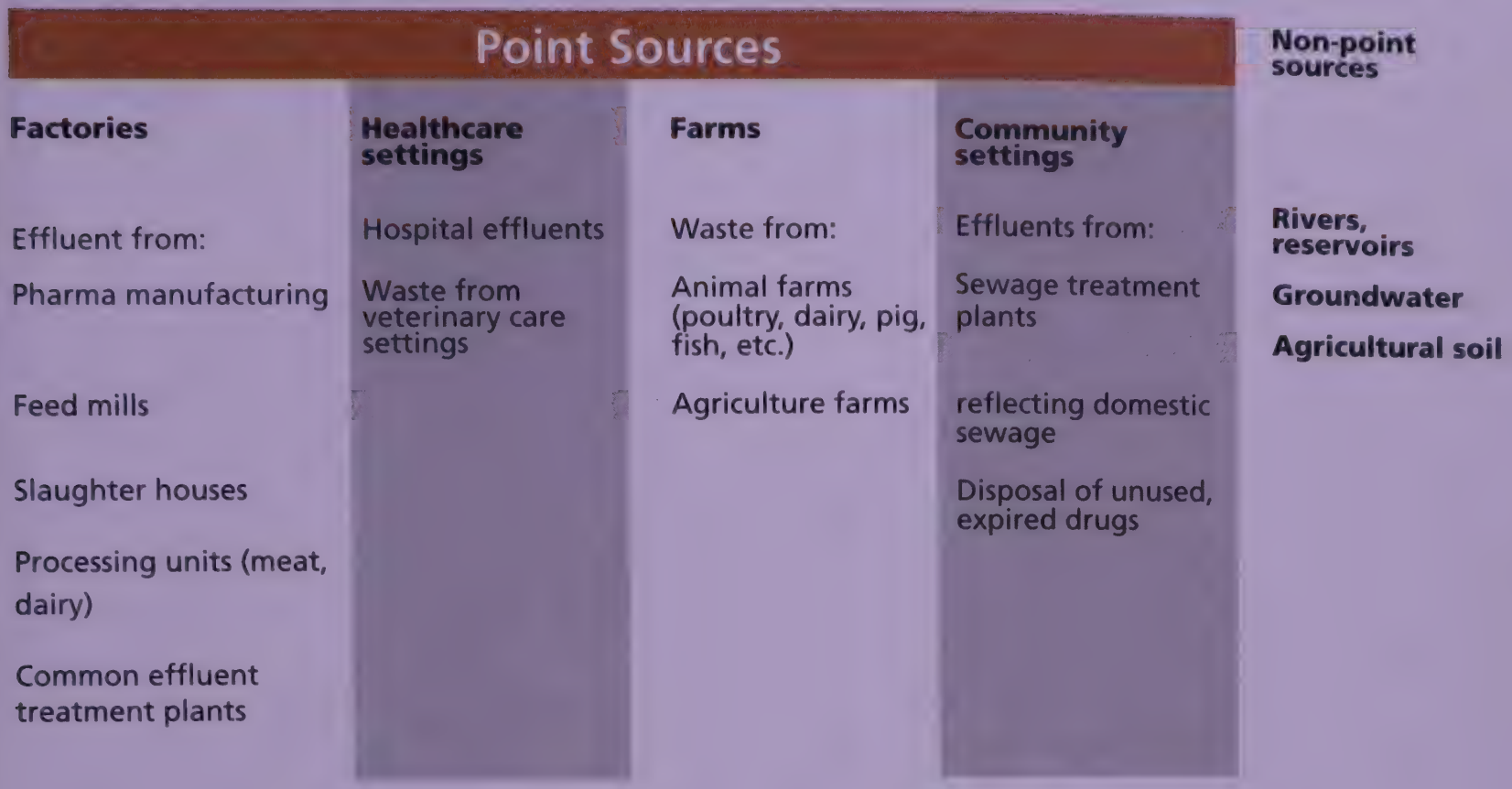
Factories are an important category of point source of waste. These include pharmaceutical manufacturing plants, feed mills, slaughter houses and industrial units processing food such as meat, dairy and fish. Samples from pharmaceutical manufacturing sites or from wastewater treatment plants receiving the manufacturing sewage have shown to contain high levels of antibiotics, ARGs, mobile genetic elements as well as resistant bacteria. Over the years, the focus of the global research community has been pharmaceutical manufacturing hubs like Hyderabad in India, since it is one of the largest producers of antibiotics in the world. For example, in 2007, Swedish researchers at the University of Gothenburg, Sweden, tested effluent samples from a wastewater treatment plant (WWTP) serving 90 bulk drug manufacturers in Patancheru near Hyderabad. The samples were found to contain high levels of enrofloxacin, norfloxacin, oxofloxacin and ciprofloxacin. The concentration of ciprofloxacin reached up to 31,000 µg/l. In 2017, researchers from Germany, tested samples from bulk drug manufacturing environments, vicinity of sewage treatment plants (STPs) on Musi river and nearby villages of the Patancheru-Bollaram industrial area in Telangana. Their study reported high concentration of antimicrobials, along with extended spectrum beta lactamase and carbapenamase producing *Enterobacteriaceae* as well as ARGs. These and many more such studies indicate how poor wastewater management by manufacturing facilities is leading to contamination of surface, ground and drinking water. Apart from pharmaceutical manufacturing sites, there have also been studies that show the presence of resistant bacteria or genes in waste from other factory settings such as slaughter houses and meat processing units. For example, multi-drug resistant *Salmonella* spp was isolated from blood and meat samples of slaughtered male cattle, buffaloes, pigs and goats by researchers at the Nagpur Veterinary College in 2016.

31,000 µg/l

was the concentration of an antibiotic, ciprofloxacin, in effluents from a wastewater treatment plant near Hyderabad.

The second set of point sources is healthcare settings. These include secondary and tertiary care hospitals and diagnostic laboratories as well as veterinary care clinics. Here too, waste has high concentration of AMR determinants. Many studies have also indicated how waste from healthcare settings contributes to AMR determinants in the environment. Indore-based R D Gardi

Structure of the environment



Medical College, Shriram Institute for Industrial Research, Karolinska Institutet and Linköping University in Sweden collaboratively conducted a study in a teaching hospital outside the city of Ujjain in 2010 to show a positive correlation between quantity of antibiotics prescribed and antibiotic residue levels in wastewater. In 2016, researchers from the Aligarh Muslim University reported the presence of ciprofloxacin resistant, extended spectrum beta lactamase producing enteric bacteria in wastewater of a medical college hospital located in Aligarh, Uttar Pradesh. A 2018 publication from the Indian Institute of Technology Delhi (IIT-D), showed that highest levels of carbapenem-resistant enteric bacteria, and resistance conferring genes (bla_{NDM-1}, *int1, and int3*) were present in hospital effluent samples, as compared to wastewater effluent samples from STPs, sewer drains or the Yamuna river in New Delhi.

Farms involved in rearing animals for food are huge reservoirs of AMR. Intensive farms characterised by high stocking densities, higher use of chemical inputs such as antibiotics and poor animal husbandry practices are of big concern as 75-90 per cent of antibiotics that are consumed by animals are excreted un-metabolised through faecal matter. The application of treated or untreated litter to agriculture fields is leading to a wider penetration of resistant bacteria or ARGs into the agricultural foodchain. Another example of such cross-sectoral dissemination of AMR determinants is the use of poultry litter in aquaculture. In the case of aquaculture, wherein antibiotics are dumped in a medium like water, the possibility of dissemination of AMR determinants into external waterbodies is higher. The other set of farms include those of crops, wherein a big part of unspent sprayed antibiotics ends up in

To cut costs, pharmaceutical manufacturers do not transfer solid waste to treatment, storage and disposal facilities. Instead, they give it to scrap dealers



Farmers use antibiotics indiscriminately against all kinds of diseases

the agricultural soil and into the waterbodies through run-off. Studies from India have also indicated linkages between farm waste and AMR in the environment. In 2009, a study from Bharathidasan University in Tiruchirappalli, Tamil Nadu, showed that transformation and conjugation could be an important mechanism for horizontal gene transfer, a mechanism of transfer of genetic elements between bacteria in poultry litter. A 2019 joint study by the Nitte University Centre for Science Education and Research, and College of Fisheries in Mangaluru showed a high incidence of multi-drug resistance among bacteria isolated from poultry, piggery and cattle farm waste, as well as water and pond sediments from aquaculture farms.

STPs that receive waste from households and communities are a source of concern—specifically those which are conventional and are not designed to address AMR. Besides, there are worries that STPs could be breeding grounds of AMR. A study conducted by the IIT-Delhi in 2017 showed the presence of high levels of beta-lactam-resistant bacteria and corresponding genes in both pre-treated and post-treated effluent samples from 12 STPs in Delhi. Another study by the National Centre for Cell Science, Pune, conducted in 2019, on wastewater samples from municipal WWTP showed pre-treated samples contained high levels of antibiotic resistant bacteria, while the bacterial load reduced drastically in post-treated effluents. Clearly, there is a need for a better understanding on waste treatment technologies to achieve high efficiency of removing ARG or ARB. Inappropriate disposal of unused antibiotic could also be leading to antibiotic pollution and adding to the environmental reservoir of AMR determinants.

GROWING GLOBAL FOCUS

UN-IACG says AMR in the environment needs to be addressed without delay

In April 2019, the United Nations-Inter Agency Coordination Group (UN-IACG) on AMR in its final report to the UN Secretary General emphasized on the growing concern about the impact of AMR on the environment. The report recognizes waste from healthcare facilities, pharmaceutical manufacturing and farms as a key driver of AMR. In order to effectively contain AMR, the report recommends ensuring best practices in waste management; developing national processes and instruments to support waste and waste management in healthcare, manufacturing and farm settings; strengthening key national systems for waste management and integrated surveillance of AMR; and increased investment and research for waste management tools.

Rivers, lakes, ponds, oceans, groundwater and soil including agriculture soil act as sinks as they receive AMR determinants from different sources. These could be termed as non-point sources, since AMR determinants through these sources re-enter into humans, animals and the foodchain. Studies have shown the prevalence of AMR determinants in groundwater, drinking water, surface water as well as in soil. For example, in 2018, researchers from multiple research institutes in Pune isolated a ceftazidime- and ciprofloxacin-resistant *E coli* from Mula-Mutha river flowing through rural Pune district and Pune city. Interestingly, even the water from the Ganga has been found to be a reservoir of microbes with antibiotic resistance genes, as was reported by a metagenomic study published by Banaras Hindu University, Varanasi, in 2019.

Prioritise the environment

Since the environment has always been at the receiving end of what we do as far as AMR is concerned, the focus so far has been on "what is going in" and not on "what is coming out". In the process, it is likely that we are missing the complete picture. The environment is not just a "sink", but also acts as a source of what comes back to us. It is time we re-think, prioritise and put the environment first. This can be achieved by adopting an AMR-centric approach to waste management that aims to control the dissemination of AMR determinants into the larger environment. That's because AMR knows no boundaries. For countries like India—which manufacture high quantities of antibiotics or are a big consumer of antibiotics—there are ample reasons to prioritise waste management to contain AMR in the environment. The MoEFCC and Central Pollution Control Board (CPCB) should, therefore, provide leadership and develop AMR-specific environmental regulations. They should adopt the precautionary principle and take action without delay.

To begin with, it is important to assess the existing laws; policies and standards; scale and spread of key waste sources; prevalent waste management practices; type and extent of waste

Sewage Treatment Plants are being considered as breeding grounds of AMR. Many studies have shown that even treated effluents of STPs have enhanced levels of resistant bacteria

SLEEPING OVER STANDARDS

Discharge limits for residual antibiotics in pharmaceutical effluents are awaiting government approval

Responding to the call made by the Indian NAP-AMR, the CPCB had developed draft standards in March 2018 for residual antibiotics in treated effluents of pharmaceutical industry (bulk drug and formulation units) and common effluent treatment plants with membership of pharma/ formulation units. These were developed in consultation with an expert committee comprising experts from government departments, pharmaceutical industry and civil society. The standards after having gone through several rounds of changes have been submitted to the Ministry of Environment, Forest and Climate Change (MoEFCC) for approval. Unfortunately, the MoEFCC have not notified these yet. CSE has been strongly advocating for the urgent need for setting discharge limits for antibiotics in pharmaceutical industry effluents ever since India decided to make its action plan, as part of the expert committee and thereafter. It is important to note that residual antibiotics in the waste of a commercial entity should be considered hazardous. Moreover, India produces and exports a major portion of global antibiotics and it need not wait for other countries to develop standards first.

generated and discharged; and, resources, capacity and infrastructure for environmental AMR surveillance and enforcement of policies.

PHARMACEUTICAL AND INDUSTRIAL WASTE: Pharmaceutical manufacturing, healthcare settings and STPs are being recognised as emerging hotspots of AMR, given the high prevalence of antibiotic residues, antibiotic resistant bacteria and ARGs detected in their effluents. In its categorisation of industries, the MoEFCC categorises the pharmaceutical industry and healthcare establishments under "red category", because of its potential to cause high pollution. Despite this, weak enforcement allows improper waste disposal in the pharmaceutical sector.

Further, environmental standards of the Central Pollution Control Board (CPCB) for industrial effluents from pharmaceutical units, STPs and CETPs also caters to general pollution parameters such as pH, dissolved oxygen, Biological Oxygen Demand (BOD), Chemical Oxygen Demand (COD), which cannot specifically address the issue of residual antibiotics.

This leaves a regulatory gap. Therefore, discharge limits for residual antibiotics in industrial effluents such as the pharmaceutical sector and other industrial and healthcare settings should be put in place. Until that happens, there will be no yard-stick to check antibiotic discharge from these point sources of concern. It is also time to device a monitoring mechanism to check for the discharge of resistant bacteria and ARGs.

1 in every six *E coli* isolates is resistant to 12 antibiotics, CSE's study found

POULTRY WASTE: The MoEFCC categorises poultry, hatchery and the pig farming industries as "green" in its industry categorisation attributing it to less pollution causing potential. At the same time, the CPCB has provided environmental guidelines for the poultry industry, which talks about management of solid waste, manure management, methods for treatment and disposal of wastewater. While these are important from the point of view of farm waste management, the guidelines are voluntary in nature, and only few states like Punjab, West Bengal, Karnataka and Haryana have so far notified these guidelines.

However, these guidelines do not talk about less risky waste management approaches such as biogas generation, validation of waste disposal process or microbial standards after waste treatment. There are also no instructions on precautions related to land application of litter/manure.

In view of AMR, the high pollution causing potential of intensive farm settings that routinely use antibiotics, needs to be recognised and reprioritised accordingly. The CPCB's guidelines for poultry farms should be strengthened and notified as a mandatory regulation. State Pollution Control Boards (SPCBs) should ensure stringent implementation. For effective AMR containment in the environment, guidelines should be strengthened considering the following:

- Land application of untreated litter must be prohibited through necessary laws, awareness and surveillance. Poultry litter must not be allowed to be used in aquaculture.
- Approaches such as biogas generation which are less risky must be preferred over land application. Big/integrated poultry farms must manage waste through in-house biogas generation plants. This should become a licensing criterion. Small poultry farmers, particularly those operating in clusters should be encouraged to develop and manage a common biogas generation plant. This should be supported by a national level programme and implemented in key poultry hubs. Other options of waste to energy conversion must also be explored.
- Proper composting for treatment of litter/manure should be encouraged under supervision. Laws related to approval of composting sites, validation of treated manure and timing of application of litter/manure should be formulated.
- The antibiotic resistance research agenda should include understanding the impact of litter/manure treatment through composting/biogas generation on resistant bacteria, and mechanisms and movements of transfer of resistance from farms to environment through waste.

AQUACULTURE WASTE: In the case of aquaculture, the CAA Guidelines provide standards for effluent discharge from farms but these again cater to general pollution parameters, and apply to brackish water farms only. The CPCB's general standards for discharge of effluents into inland surface water, land for irrigation, marine coastal areas also cater to similar parameters and are applicable to both freshwater and brackish water farms.

But both CAA guidelines and CPCB's general standards do not specifically address the presence of antibiotics or antibiotic resistant bacteria in aquaculture farm effluents. The CPCB should formulate regulations which underline the importance of appropriate farm waste treatment, while SPCBs should adequately monitor waste management. All fish farms should be registered, and environment assessment should be integral to such a registration process.

UNUSED DRUG DISPOSAL: The safe and appropriate disposal of unused drugs, including antibiotics is important towards limiting the release of residual antibiotics in environment. As per the Solid Waste Management Rules (SWM) 2016, the Municipal Corporation is mandated to collect the medicinal waste from households and market places, separately from the rest of the domestic waste. Only few cities in India have however adopted the SWM bye laws, and many are yet to adopt. Moreover, implementation on the ground, for example in Delhi NCR, is inadequate thereby leading to lack of proper segregation of waste at source and inappropriate disposal.

The CPCB should introduce a provision for extended producer responsibility (EPR) that would make drug manufacturers responsible and accountable for safe disposal of unused drugs. Such a provision would facilitate both branded and generic drugs to be smoothly taken back through the existing supply chains. The Central Drugs Standard Control Organisation (CDSCO) should also ascertain revision of the Drugs and Cosmetics Act, in parallel, to align with the new EPR provision. Ensuring effective implementation of EPR provision would require participation from consumers as well. But under such a provision, consumers may not be mandated to safely dispose unused drugs. So the municipal corporation should ensure efficient segregation of medicinal waste at source. The need for EPR provision has already been recognized in India's NAP-AMR. The state of Kerala has implemented its own drug take-back program. Operation 'Program on Removal of Unused Drugs (PROUD)' is a first of its kind programme in India, aimed at the collection of unused or expired capsules, tablets, oral liquids, ointments, and empty strips from household settings. It is a joint initiative of the Department of Drug Control, Government of Kerala and the All Kerala Chemists and Druggists Association, to address unsafe and unscientific practices of drug disposal. The programme was launched by the Hon'ble Minister for Health and Social Justice, Smt. K.K. Shyalaja Teacher, in March 2019. Presently being piloted in Thiruvananthapuram, around 35 collection bins have been placed at select retail pharmacies in various parts of the district, particularly around central locations, such as hospitals etc. The filled bins are planned to be collected on a monthly basis by Kudumbashree (a Government of Kerala programme) following which it will

India's booming pharmaceutical industry is known to dump antibiotic residues in the environment



The CPCB should introduce a provision for extended producer responsibility (EPR) that would make drug manufacturers responsible and accountable for safe disposal of unused drugs

be handed over to the Mangalore-based Common Biomedical Waste Treatment Facility, Ramky Energy and Environment Ltd. for segregation and disposal by incineration . Other states must also come forward, recognize the need for EPR in their state action plans and and consider taking similar initiatives.

SURVEILLANCE AND RESEARCH: The surveillance of AMR in the environment will be crucial for a long-term AMR containment strategy. This should include surveillance of antibiotic resistant bacteria, ARGs and antibiotic residues, across point and non-point sources. While surveillance at point sources could be a routine process, surveillance across non-point sources could initially be a part of the AMR research agenda, and this should also be formulated. The design of environmental surveillance should be further integrated with AMR surveillance in human, animal, food and agriculture sectors. To achieve this, an integrated surveillance strategy or framework—that provides guidance on key antibiotics, bacteria and genes, sample type, size, and locations—should be developed. The public availability of data also needs to be ensured. Environmental AMR surveillance should be prioritised and implemented in a phased and progressive manner, which would mean that the type of bacteria, genes and the number of antibiotics to be used could be gradually increased over time.

On the research front, genomic and metagenomic studies can be carried out for an evolved understanding of AMR transmission in the environment. This will not only help set the stage for gene and molecular level understanding of AMR in the environment, but it will also help develop a strong case for policymakers and inform future policy and plans.

DISPOSAL SANS SCRUTINY

Unused antibiotics continue to be dumped in the open. This is leading to antibiotic pollution

DIVYA KHATTER, RAJESHWARI SINHA, AMIT KHURANA

THE PRACTICE came as a rude shock to Bachaspatimayum Debkumari when she returned to India after spending five years in Belgium. The tiny European country is known for managing its waste well. People are particularly careful while disposing hazardous substances like expired and unused drugs. "I used to store unused drugs in a box and take it to a drug store for disposal," says Debkumari, who now lives in Delhi's Vasant Kunj. "But here, even if I carefully segregate domestic waste and pack unused drugs in separate bin bags, garbage collectors mix those with general waste and dump it in landfills," she adds.

Being a researcher in biological sciences, Debkumari is aware of the hazards pharmaceutical products can have on the environment. Studies show that careless discharge of drugs, particularly antibiotics, into the environment could be spurring the development of superbugs that are resistant to most antimicrobial drugs. The Municipal Solid Waste Management (MSWM) Rules, 2016 categorises expired drugs as domestic hazardous waste and requires those to be segregated and stored in separate bins and disposed in accordance with the Biomedical Waste Management Rules, 2016, which says that the drugs must be incinerated at high temperatures. But are these guidelines being followed? Researchers of the Delhi-based non-profit Centre for Science and Environment (CSE) interviewed residents and drug store owners in Delhi and the National Capital Region (NCR) and visited dumpyards. The findings are disconcerting.

While most people interviewed by CSE were unaware of the impact of careless disposal of unused drugs, some had only a vague idea about it. "Medicines should not be dumped in the open as stray animals tend to feed on those and get poisoned," says Nagesh Parmar, a homemaker from Faridabad, Haryana. Yet, she disposes unused drugs along with domestic waste, which gets picked up by an informal collector and dumped along a *nallah* or at the collection site of Municipal Corporation Faridabad (MCF).

When CSE researchers visited the collection site, they found syrup bottles and tablets without packaging scattered all over, with animals and humans combing through heaps of trash for food and livelihood. "From here, the waste goes to Bandhwari dumpsite located 20 km from Gurugram. At the dumpsite, the waste is spread around and levelled using rollers," says Devendra of Ecogreen Energy, an integrated waste management company that has tied up with MCF for collecting waste from the twin cities. A 2017 survey by the Central Pollution Control Board (CPCB) shows leachate from the dumpsite, which receives 1,200 tonnes of waste a day, has polluted groundwater in the surrounding areas. "Leaching of pharmaceutical substances into groundwater and their spread can be a potential source of antibiotic pollution and lead to antimicrobial resistance," says Satish Sinha, associate director at Delhi-based non-profit Toxics Link. Such poor management of hazardous waste is primarily due to lax enforcement of MSWM rules. Several cities are yet to adopt MSWM by-laws that mandate segregation, storage, delivery and collection

Key drug take-back programmes in Europe

Country	Name of drug take-back scheme	Year of launch	Source of funding
France	Cyclamed	1993*	Manufacturer
Belgium	Bonusage	2000	Manufacturer, wholesaler and pharmacist
Portugal	Sistema Integrado de Gestão de Resíduous de Embalagens de Medicamentos (SIGREM)	2001	Members of the pharmaceutical associations, including community pharmacies, pharmaceutical manufacturers, pharmaceutical distributors, and chemical and pharmaceutical importers
Spain	SIGRE Medicines and the Environment	2001	Manufacturer
Hungary	Recyclomed	2005	Manufacturer
Sweden	Sveriges Farmaceuter	2009	Manufacturer and municipality

*In 1993, Cyclamed was launched as a voluntary programme and it was mandated under law in 2007

of municipal solid waste, including discarded medicines. A senior official at the North Delhi Municipal Corporation, however, says, "It will take us a few years before we achieve wet and dry waste segregation. Hazardous waste segregation will have to wait."

But what about those who deal with drugs in large quantities on a daily basis? To understand this, CSE researchers visited wholesalers and retailers across Delhi-NCR. At Bhagirath Palace, the largest wholesale drug market in the country, CSE researchers found all kinds of drugs strewn on the streets, most of them were antibiotics. "Every morning, we clean up the streets and dump discarded drugs at the municipal dumpsite," says Dinesh, a waste picker. Dealers say branded drugs are returned to suppliers once they near the expiry date. But generic drugs cannot be returned. The only option is to throw them away. "Even cut strips are not taken back," says the owner of a drug store at Yusuf Sarai.

The practice does not change much beyond Delhi's border. "We burn drugs, dump them in *nallahs* or dispose them along with general waste," says Shanvaj Khan, a pharmacist in Faridabad. Surprisingly, burning is considered a legitimate way of disposal by some people. A sales boy at a medical store at Sharma market, Noida, Uttar Pradesh (UP), says, "We ensure to make a video of burning drugs as a proof of destruction for drug inspectors." At the wholesale market in Nai Basti, Ghaziabad, another city in UP, Naveen, owner of RIS Pharma, prefers disposing the expired drugs at municipal dump sites.

A senior official at the drug regulatory body of India, the Central Drugs Standard Control Organization (CDSCO), is confident that the Drugs and Cosmetics (D&C) Act, 1940, has laid down all provisions to deal with unused drugs in the supply chain. But an analysis of the law shows that Schedule M of D&C Act talks only about separate storage of expired drugs and is silent on their safe disposal.

The National Formulary of India (NFI), a manual by the Indian Pharmacopoeia Commission, suggests the return of unused drugs from retailers to wholesalers and producers. But since it is non-binding, drug inspectors do not perform regulatory checks. For disposal of drugs in small quantities, NFI



recommends cumbersome ways like mixing those with used tea and coffee grind before discarding. Under MSWM by-laws, municipal corporations are required to collect unused drugs from retailers and wholesalers in a separate black bin, but this too is lacking.

Worldwide, governments have been implementing drug take-back programmes for over a decade now, with Europe taking the lead. A pioneer programme in France called Cyclamed was launched in 1993 (see "Key drug take-back programmes in Europe", *p75*). Cyclamed brought together major pharmaceutical stakeholders such as individuals, retail pharmacies, wholesalers and companies under the same umbrella. Under this programme, people are supposed to deposit unused drugs without packaging in Cyclamed cartons at a nearby pharmacy. The wholesalers then collect these cartons and store them in huge waste containers located at their premises. Once full, these containers are transported by carriers to the waste treatment plants where a waste tracking slip—indicating the tonnage of drugs recovered—is issued. The waste is incinerated with energy recovery. Typically, these drug take-back programmes are based on a model where a third party—the producer responsibility organisation (PRO)—helps a producer collect, recycle and properly dispose its products under extended producer responsibility (EPR). Funding is sourced either from the manufacturer or from all those involved in the supply chain.

"In Belgium, cost sharing among pharmacists, wholesalers and the industry is a legal responsibility," says Kristof Bonnarens, research manager at pharma.be, a group of pharma companies in Belgium. "The philosophy is medicines are not common household items. So, they should follow the same supply chain

back even after disposal," says Bonnarens. "The practice prevents secondary trade of medicines," says András Miklósi of Recyclomed, a drug take-back PRO in Hungary.

In March 2019, Kerala launched a similar initiative on a pilot basis. Named, Program on Removal of Unused Drugs (PROUD), this joint initiative of Kerala's State Drug Control Department and the All Kerala Chemists and Druggists Association (AKCDA) aims to address improper disposal of drugs by households. Under PROUD, locked kiosks or collection bins have been placed near select pharmacies in central locations. Initially, around 35 bins were placed outside various pharmacies in Thiruvananthapuram district. The programme will be expanded and more number of bins would be placed covering more areas. People have been informed and encouraged to drop their unused pharmaceutical products in these bins. The medicinal waste including tablets, ampoules, sprays and syrups are collected monthly by Kudumbashree, a government of Kerala programme. The waste is then sent to a common biomedical waste treatment facility run by Ramky Energy and Environment Ltd in Mangalore for segregation and disposal by incineration. By October, some five tonnes of unused drugs were collected under PROUD. As of now, A K Mohan, president of AKCDA has agreed to fund the initiative for a year at ₹10 lakh. CSE researchers reached out to a few officials working with pharma companies and asked whether they would fund collection and disposal of unused drugs under EPR. Some agreed while others expressed reluctance citing financial crunch.

This is disappointing at a time when the National Action Plan on Antimicrobial Resistance (NAP-AMR) recognises the need for a provision like EPR. Recently, while urging states to treat AMR as a priority, NAP-AMR has called for development of policies and implementation mechanisms for the safe disposal of unused and expired antibiotics.

States should take up pilot drug take-back projects like PROUD. They should also incorporate EPR in their state action plans

For proper disposal of unused drugs, particularly antibiotics, CSE offers a slew of recommendations to the government. It says CPCB should introduce an EPR provision that would make both branded and generic drug manufacturers responsible and accountable for the disposal of unused drugs. An EPR provision would enable smooth take-back of branded and generic drugs through the supply chains, as compared to the complicated process of segregating medicines from municipal waste. Manufacturers could execute the entire process of collection, transport and disposal themselves or by outsourcing it to a PRO. Dinabandhu Gouda, a scientist at CPCB, says a drug take-back programme is very much feasible in the country.

CDSCO should consider revision of the Drugs and Cosmetics Act so that it aligns with the new EPR provision. Moreover, ensuring effective implementation of EPR would require participation from consumers. But under such a provision, consumers may not be mandated to safely dispose unused drugs. So municipal corporations should work towards efficient segregation of hazardous medicinal waste at the source and create awareness. Involvement of other stakeholders like drug regulatory bodies, pollution control boards, local bodies, civil society and self-help groups are vital for the proper implementation of EPR on the ground. States should consider piloting drug take-back projects like PROUD. They should also incorporate EPR in their state action plans.

Hidden dangers

ROHAN GUPTA identifies household products that have chemicals that trigger resistance to antibiotics



3

PACKAGING MATERIAL

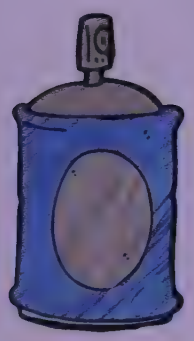
Antibiotic ingredients in packaging materials kill or inhibit pathogenic microorganisms that can contaminate food such as bakery products, dairy, fruits and meat. Popular antimicrobial agents used for this purpose include algicides, nactericides and fungicides. Anti-microbial packaging can be a $11.88 billion market globally by 2024. Currently, it is a $7.65 billion market.



2

DETERGENTS, SOAPS, KITCHEN SPRAYS

Triclosan, an antimicrobial active ingredient is commonly found in household products. As extensive use may lead to antibiotic resistance, food and drug authorities like USFDA have banned *triclosan* along with 18 other antimicrobial chemicals from such products.

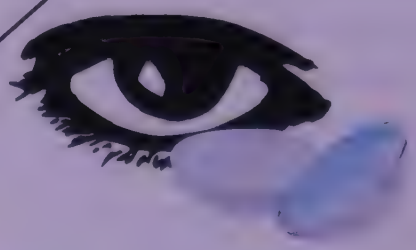


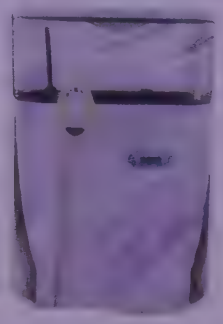


1

DEODORANTS AND ANTIPERSPIRANTS

Deodorants contain specially developed antimicrobial agents like *triclosan* and *polyhexamethylene biguanide*, apart from aluminum salts. Everyday use can lead to development of resistance in the exposed microbes. Market researches show that the global antiperspirant and deodorant market is likely to reach $92.7 billion by 2024 and efforts should be made to reverse this trend.





10

ANTIMICROBIAL CONTACT LENSES

To minimise the risk of infections in contact lens wearers, antimicrobial contact lenses are being developed. Some pending patents contain silver as active ingredient.

9

WATER PURIFIERS

Antimicrobial filters in water purifiers have bacteriostatic filter cartridges. A silver-based material or zinc nanoparticles are some of the agents used in water filteration. Ceramic filters infused with silver are also used.



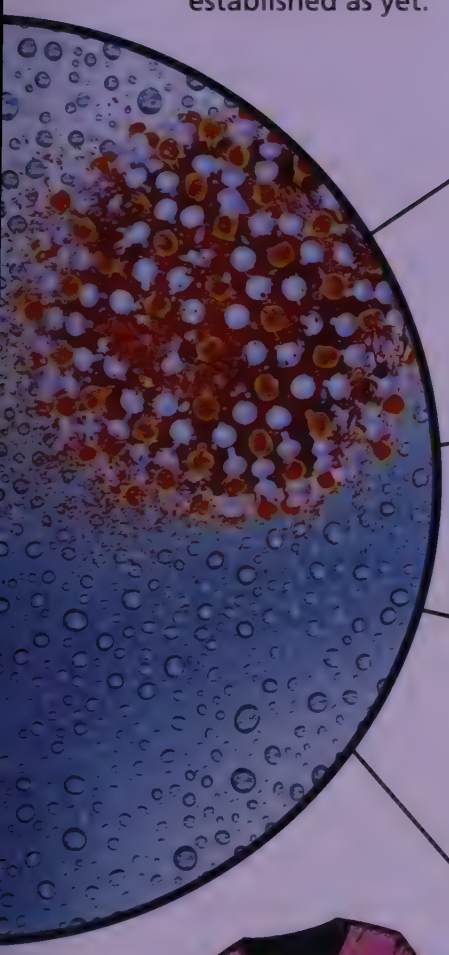
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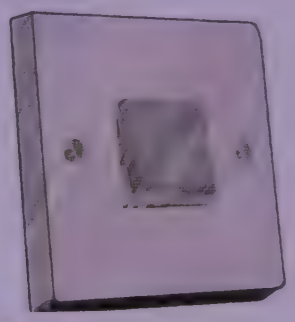
PERSONAL HYGIENE PRODUCTS Anti-acne face washes kill bacteria that cause acne. Common active ingredients used are benozoyl peroxide, salicylic acid, alpha hydroxy acids and sulphur. In mouthwashes, chlorhexidine is the most common active ingredient. The link between chlorhexidine and resistance is not established as yet.



5

ANTIMICROBIAL SANITARY NAPKINS An Indian patent related to antimicrobial sanitary napkins is pending. The proposed product contains silver nanoparticles or a silver thin film impregnated in the polymeric material among the multiple layers of absorbent material of the sanitary napkin.





6

ELECTRIC SWITCHES Antimicrobial switches contain silver ions as active ingredients. The silver compound prevents the growth of microbes on the surface plate.



8

CLOTHES Antimicrobial clothing is used to control body odour. These use silver ions, ammonium compounds, polyhexamethylene biguanides, triclosan and chitosan.



7

PAINT Antimicrobial paint are being marketed as protection against microbes. According to a study, antimicrobial paint typically killed most bacteria proliferating in the indoor environment within 24 hours. But these can lead to antibiotic resistance. Active ingredients used are silver and gold nanoparticles, crystal violet and ammonium salts.

A NECESSITY WE IGNORE

Use of technologies to detect, control and contain antibiotic residues must be made mandatory

INDUMATHI M NAMBI

THERE IS mounting evidence that residues of antibiotics are present in rivers and our drinking water. A recent study by researchers from the Banaras Hindu University (BHU)—who tested at five of the ghats in Varanasi—revealed that antibiotic as well as metal-resistant bacteria are present in the Ganga. This should not come as a surprise considering that the river gets over 309.8 million litres of treated and untreated domestic waste daily. The study was carried out by researchers from the Molecular Ecology Laboratory, Centre of Advanced Study in Botany, BHU, and the results were published in *Environmental Pollution* in March 2019.

Even way back in 2011, research showed the presence of antibiotic-resistant microbes in drinking water and sewage in New Delhi. This was published in *The Lancet Infectious Diseases* and showed that the resistance was due to the enzyme New Delhi metallo-beta-lactamase 1 (NDM-1). This is the result of increasing antibiotic consumption for therapeutic and veterinary application in India.

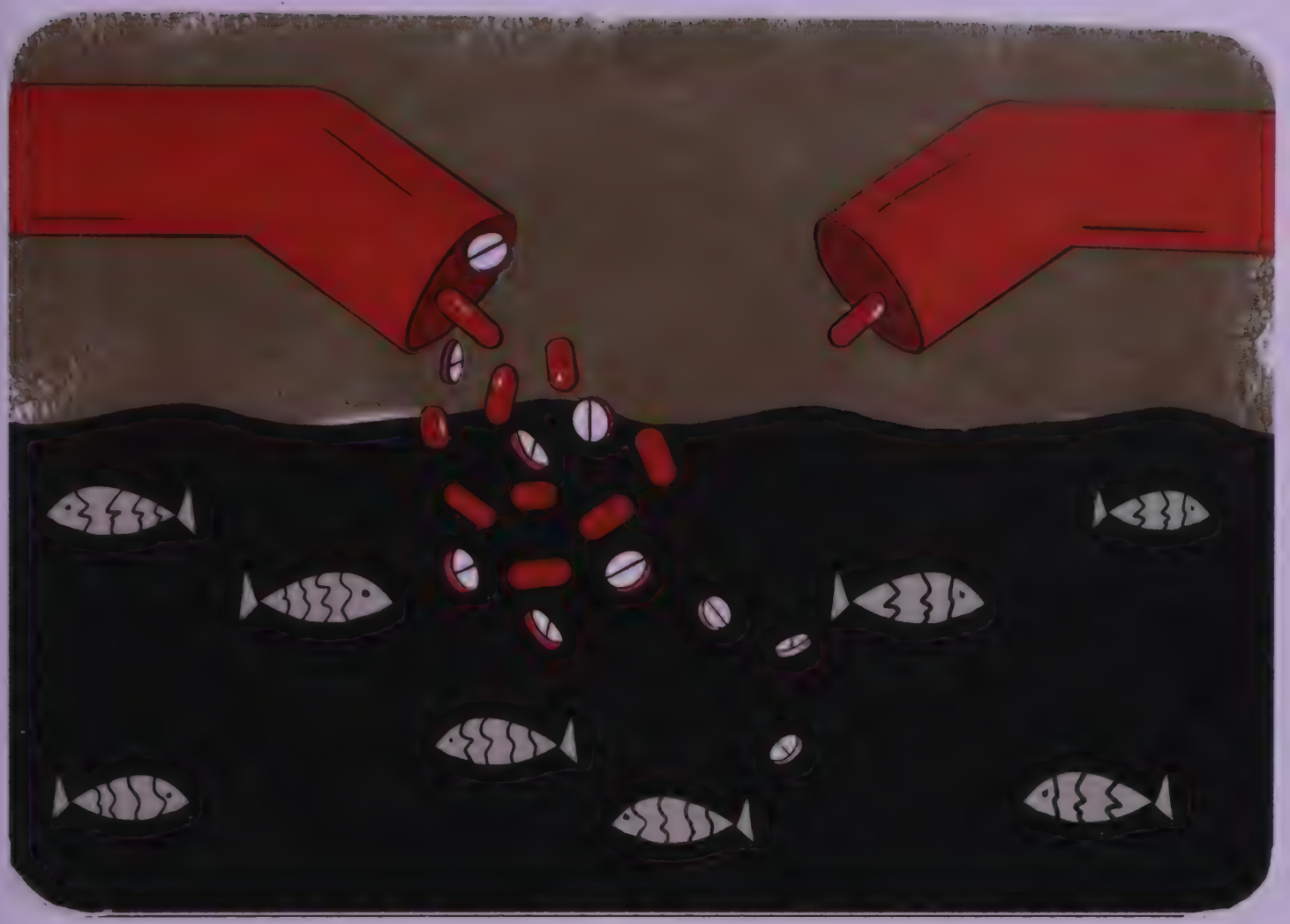
The pattern of antibiotic consumption, prescriptive quantity and availability reflects in antibiotic concentrations and antibiotic resistance in groundwater, surface water, river water, sediments and wastewater. About 30-90 per cent of the antibiotics consumed are not completely metabolised and are excreted via urine and feces. Gut bacteria, especially *E coli*, may develop resistance to antibiotics consumed and harbour resistance genes, which can be transferred horizontally to other gut bacteria. Un-metabolised antibiotics, byproducts of metabolised antibiotics and resistant gut bacteria excreted find their way to sewage treatment plants (STPs).

At the same time, India is the fourth largest consumer of veterinary antibiotics. Antibiotics are used in livestock, aquaculture, apiary, pig farming, both for therapeutic and non-therapeutic applications like disease prevention and as growth promoters. Like humans, the un-metabolised antibiotics and resistant bacteria are excreted via urine and faeces of animals too. Additionally, animal waste is also used as a preferred source of manure/fertiliser for agriculture lands. Leaching out and flooding of lands often washes the antibiotic residues off into ground and surface water sources respectively.

High concentration of Ciprofloxacin has been reported in the effluents of common effluent treatment facilities of bulk drug manufacturers. National Science Foundation funded IIT Madras and Virginia Tech studies on wastewater treatment plants in Chennai, which revealed high concentrations of antibiotics such as macrolides, quinolones in the order of 100s of parts per billion (ppb). The IIT Madras group monitored waterbodies and groundwater in and around Chennai and indicated high concentration, as much as 100-300 ppb, of ciprofloxacin, trimethoprim and triclosan in Coovum river, lakes in the vicinity of pharmaceutical plants and outlets of wastewater treatment plants.

The culprits

Hospitals and bulk-drug manufactures play an important role in the spread of AMR. While the former introduces both antibiotics and antibiotic resistant bacteria (ARB), the latter introduces high concentrations of antibiotics



into the environment. Hospital effluents also contain high concentration of antibiotic resistant genes (ARGs). Central wastewater treatment for hospital effluents in India is uncommon and it is reported that less than 45 per cent of hospitals have wastewater treatment facility. Most of the hospital effluents in India drain into domestic sewer system and reach STPs. Discharge of hospital effluents into domestic sewers increases the percentage of resistant bacteria there by 95 per cent.

Wastewater treatment may provide the right environment for resistant gene transfer as most of the treatment strategies involves one or the other biological methods that increase the microbial load along with the genetic material load. The sludge containing organic matter and microbes is separated from the treated water and commonly used as soil amendments. Apart from proliferation during biological treatment, bacteria encounter more antibiotics at sub-lethal concentrations and develop resistant to them.

Sludge from treatment technologies is less studied for occurrence of antibiotics, ARB and ARG. As sludge is used as soil amendment in agricultural fields, treatment of sludge should be prioritised and protocols must be established.

Conventional treatment technologies like extended aerobic process, activated sludge process and artificially constructed wetlands significantly reduce antibiotics that are biodegradable though antibiotic removal efficiency by these processes is lower compared to other pharmaceuticals. Synthetic and recalcitrant antibiotics cannot be removed by conventional treatment technologies.

Additionally, secondary treatment can ensure reduction in viable microbial load, but not the resistant genes. ARG and ARB in effluents decreases during processes like anaerobic, anoxic, sequential anaerobic-aerobic, membrane bioreactors (MBR), constructed wetlands and rotary biological contractors to some extent. It is seen that coagulation technologies reduces ARG to some extent. Some reports suggest that during chlorination, 20-60 per cent reduction and deactivation of ARGs is achieved.

Advanced disinfection along with advanced oxidation treatment for removing antibiotics should be introduced in water treatment plants

Tertiary treatment like disinfection also reduces microbial load to meet discharge or reuse standards rather than genetic material. Disinfection of treated wastewater kills bacteria but during this process ARGs in plasmid or genomic DNA are released into the water.

Other than the use of sludge as manure, treated/partially treated water is widely used for irrigation of agriculture lands due to water shortage in some parts of India. In such situation, there is a high probability that farmers and livestock are directly exposed to ARB and ARG and serve as a pathway for ARB disease spread among farming communities.

Due to water shortage in urban areas, sometimes treated wastewater also finds its way in gardening and to flush toilets. This too may serve as a pathway to introduce resistant bacteria into indoor air and soil environment, which will severely impact the habitants, children and farmers who are likely to get exposed.

Technologies to the rescue

From the prevalence of antibiotics and AMR in water bodies to effluents of treatment plants, it is evident that we need better control mechanisms of these emerging threats. This should be developed and established at every source.

Tertiary treatment strategies like adsorption and advanced oxidation process (AOP)— which oxidise free radicals to decontaminate wastewater—are widely believed to remove antibiotics effectively, but right now that is happening only on a laboratory scale. As mentioned earlier, disinfection alone is not adequate since horizontal gene transfer of ARGs from dead cells can propagate resistance to other populations. AOP processes like UV/H2O2, UV/H2O2/Fe2+ and ozonation completely degrades antibiotics. UV/chlorination and ozonation are reported to be effective in eliminating ARG and ARB rather than either of the methods when applied individually. Antimicrobial nanotechnology is an emerging technology which is proving effective in treating antibiotics, ARB and ARGs. Recently, the application of bio-char as a soil amendment was found to prevent antibiotics, ARB and ARG accumulation in vegetables. However, this process is quite expensive compared to a conventional treatment method and cannot be implemented on a large-scale. These have been mostly implemented in Europe where there is water shortage and reuse of treated wastewater is gaining popularity.

For countries like India, low cost, low energy methods are needed. IIT Madras recently developed an electrochemical-based technology, which removes almost 99 per cent of recalcitrant-antibiotics, ARB and ARGs using novel electrodes with minimum power consumption. Such disinfection strategies should be deployed in wastewater treatment plants before treated water is released into water bodies or reused.

Advanced disinfection along with advanced oxidation treatment for removing antibiotics should be introduced in water treatment plants. Other than this, there should be mandatory surveillance of all effluent from sources such as poultry, dairy, aquaculture, hospital and pharmaceutical and of air, water and soil environment where the effluent is discharged to identify prevalence of AMR genes. This will also enable regulating antibiotic prescriptions particularly those for which high level of resistance is exhibited in the environment. Such regulations and retrofitting water and wastewater treatment plants will in the long run mitigate this emerging threat to humans and the health of ecosystems.

ANTIBIOTICS IN OUR FOOD

Indiscriminate use of antibiotics in food production—honey, chicken meat, fish and milk—is contaminating the foodchain and leading to increased antibiotic resistance

AMIT KHURANA, RAJESHWARI SINHA



ANTIBIOTICS, WHICH were originally designed for treatment of humans, are grossly misused in food-animals and crops. In food-animals, apart from therapeutic purposes—that is, to treat sick animals—antibiotics are used for growth promotion and disease prevention. Growth promotion refers to the use of antibiotics to increase the rate of weight gain and/or feed utilisation by food-animals. The use of antibiotics allows farmers to attain lower Feed Conversion Ratio (FCR), implying that less feed is required to attain maximum weight. Antibiotics are also routinely administered to food-animals, mostly through water, for mass disease prevention even when any clinical sign of the disease are absent. Such prophylactic use also masks the ill-effects of poor animal husbandry practices such as poor biosecurity and inappropriate waste management. Antibiotics in feed can play a dual role of promoting growth and preventing diseases.

But this use of antibiotics in food has linkages to antimicrobial resistance (AMR), as low-doses of antibiotics used for long duration in food-producing animals—such as poultry, dairy or fish—favours selection of resistance and leads to the emergence of resistant bacteria in animals. Resistant bacteria can proliferate and the resistance genes can be transferred to other species of bacteria present in animals and make them resistant.

Such resistant bacteria can be transferred to humans through direct contact with live animals or carcass at farms and slaughterhouses; consumption of meat and food; and, via environmental contamination of soil, water and air through animal excreta. Antibiotic residues entering into humans through the consumption of residue-contaminated food may put selective pressure in the bacteria present in humans and lead to resistance. The Centre for Science and Environment (CSE), a New Delhi-based non-profit, has been conducting studies for nearly a decade through its Environment Monitoring Laboratory to highlight antibiotic misuse in various sectors.

Antibiotics in honey

In 2010, the European Union banned Indian honey because it was contaminated with antibiotics. To prevent damage to exports, the Exports Inspection Council (EIC) formulated "Level of Action"—similar to standards—for antibiotics in exported honey. If a sample was found to contain antibiotics beyond the Level of Action, it was deemed non-compliant. However, the EIC standards, did not apply to honey sold in Indian domestic markets.

Recognising this regulatory void, CSE had decided to test honey which was available for domestic consumption. CSE tested 12 samples of branded honey bought from Delhi in 2010—10 domestic and two imported honey samples. These were tested for the presence of six antibiotics—oxytetracycline, chloramphenicol, ampicillin, enrofloxacin, ciprofloxacin and erythromycin. CSE found that 11 of the 12 samples of honey that were tested, contained multiple antibiotics.

11

of the 12 honey samples from Indian markets that CSE tested contained multiple antibiotics

The samples that tested positive for tetracyclines and chloramphenicol failed to meet the standards set by EIC for exported honey. In 2010, no such EIC standards existed for ampicillin, enrofloxacin, ciprofloxacin and erythromycin. Multiple antibiotics were detected in all domestic and imported brands of honey tested. The highest number of antibiotics were detected in imported Nectaflor Natural Blossom Honey.

There is another aspect as to why antibiotics are being indiscriminately used in the

Antibiotic administration starts well before the lifecycle of a broiler chicken. While preventive doses were given to day-old-chicks, parent stocks of broilers were routinely exposed to antibiotics at parent breeder farms

honey sector. In 1965, the Punjab Agriculture University introduced the Italian bee species, *Apis mellifera*, in the country. Till then, honey was sourced from bee colonies of native species like the Indian rock bee (*Apis dorsata*), Indian honey bee (*Apis cerana*) and the dwarf honey bee (*Apis florae*). The Italian bee species soon replaced native bees in the apiaries of Himachal Pradesh, Punjab, Haryana, Uttar Pradesh and the erstwhile Jammu and Kashmir as the honey yield from their hives was higher. With a change in the bee species, their disease profile also changed. The Italian bees are believed to have a poor defence mechanism. Bee keepers were found to use antibiotics, mainly tetracyclines, to manage diseases such as brood disease, for which the antibiotic was mixed with sugar and left on the bee boxes for the bees to feed on. Notably, antibiotic use is not recommended during honey flow period, but bee keepers turned to antibiotics due to threat of diseases and growing demand for honey.

Other studies too have reported similar findings. Residues of oxytetracycline were detected in seven branded honey samples and a raw honey sample collected from local markets of Guntur district in Andhra Pradesh. The study was jointly done by researchers at the VSR and NVR College, Tenali, and Medarametla Anjamma Mastan Rao College of Pharmacy, Narasaraopet in Andhra Pradesh. It was published in the *International Research Journal of Biological Sciences* in 2015. Researchers at the University of Aden and National Quality Control Laboratory in Yemen found oxytetracycline residues in two of three Kashmiri honey samples tested at 9,033 and 3,430 parts per billion (ppb) respectively. The study, which was published in the *Journal of Agricultural Science and Technology* in 2016, says that oxytetracycline positive samples were imported from Kashmir and were available in the local markets of Yemen.

Another recent study done by researchers from CSK HP Agricultural University in Palampur, Himachal Pradesh reported the presence of oxytetracycline residues in 15.3 per cent honey samples collected from various retail markets of India. The residues were found in the range of 9-69 ppb, which is way above the threshold set by the Food Safety Standards Authority of India (FSSAI). The study was published in the *Journal of Apicultural Research* in October 2019.

Antibiotics in chicken meat

The poultry sector in India too has undergone a major change in structure and operation over the past two decades. From being a mere backyard activity, rearing broilers (those grown for meat) and layers (the ones grown for laying eggs) has grown into a major commercial activity, with presence of large integrated players and successful implementation of contract poultry farming on a large-scale.

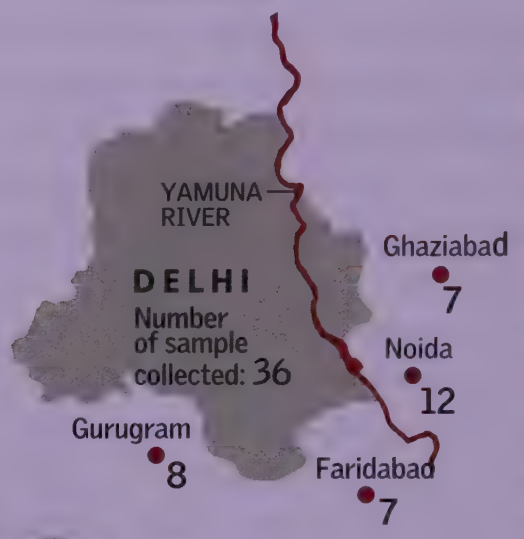
In 2014, CSE tested chicken sold in Delhi-National Capital Region (Delhi-NCR) for the presence of antibiotics. CSE bought 70 samples of chicken from retail outlets in Delhi-NCR in two batches and tested them for six antibiotics—oxytetracycline, chlortetracycline,

Know the chicken you eat

CSE found antibiotics in 40% of chicken samples from most of the locations tested in Delhi-NCR

Antibiotics	Chicken with antibiotics	Level of antibiotic (in µg/kg)
Oxytetracycline	11.4%	8.25-15.16
Chlortetracycline	1.4%	10.20
Doxycycline	14.3%	11.94-20.66
Enrofloxacin	20%	3.37-131.75
Ciprofloxacin	14.3%	3.55-64.59

Antibiotics were found in 12 of 16 locations in Delhi-NCR

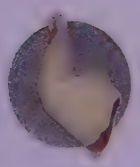


DETAILS

- They were found in all types of tissues tested: muscles, kidney and liver
- 22.9% chickens had one antibiotic
- 17% had more than one antibiotic
- Antibiotics were present in the range of 3.37-131.75 g/kg

LEVELS OF ANTIBIOTICS IN DIFFERENT PARTS OF CHICKEN

(Figures in µg/kg)



Muscle

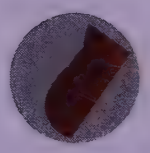
8.45-13.60

10.2

14.61-20.66

3.84-58.06

3.55-26.27



Kidney

8.25

ND

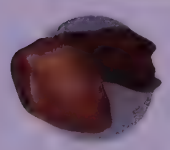
15.73

ND

ND

- Oxytetracycline
- Chlortetracycline
- Doxycycline
- Enrofloxacin
- Ciprofloxacin

ND Not detected



Liver

9.13

ND

11.94

3.37-131.75

7.55-64.59

5 of 6 antibiotics tested were present in chicken samples

Fluoroquinolone antibiotics were found in **28.6%** chicken samples

Tetracycline antibiotics were found in **14.3%** chicken samples



METHODOLOGY

Each chicken meat sample was analysed in triplicate for six antibiotics of three classes using High Performance Liquid Chromatograph (HPLC) with Diode Array Detector (DAD) and Fluorescence Detector (FLD). Methodologies used were based on published methods and validated. Environment Monitoring Laboratory is an ISO 9001:2008 accredited laboratory.



doxycycline, enrofloxacin, ciprofloxacin and neomycin. CSE found 40 per cent of the samples contained antibiotics (see "Know the chicken you eat", p86). Residues of five of the six antibiotics were present in these chicken samples. The antibiotic residues were detected in all the three tissues—muscle, liver and kidney.

To understand how antibiotic residues were found in chicken, CSE studied the practice of raising poultry through a field study in Haryana, which is the fourth largest producer of poultry meat in India. The study found that antibiotic administration started well before the lifecycle of a broiler chicken. While preventive doses were given to day-old-chicks (DoCs) at broiler farms, parent stocks of broilers were routinely exposed to antibiotics at parent breeder farms. Non-therapeutic exposure to grandparent stocks was not ruled out either.

It was also found that the use of antibiotic growth promoters (AGPs) was an integral part of broiler farming. Broilers were fed with antibiotic-laden feed throughout their lifecycle. Feed with different AGPs was easily available and feed mills preferred making feed with AGPs. Routine preventive administration of antibiotics was also a common practice. Easy availability of unlicensed antibiotics is known to have influenced this practice.

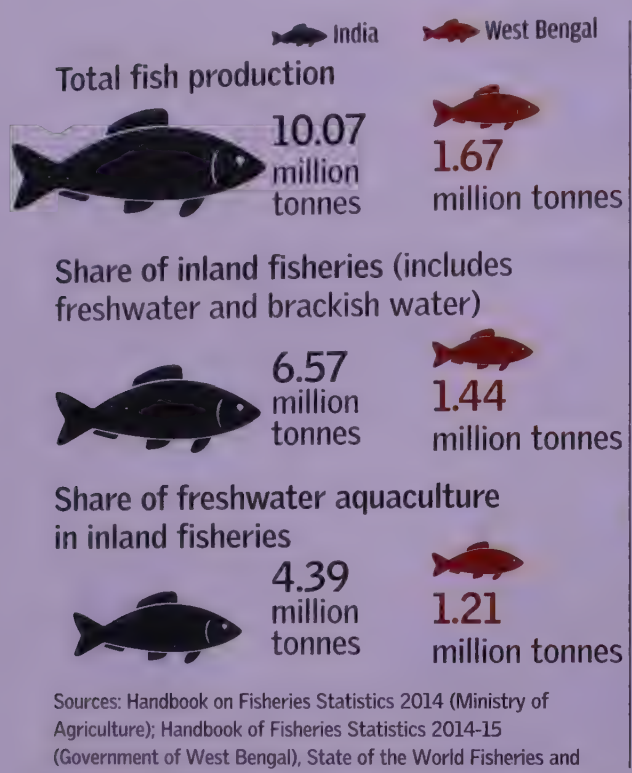
Most famers did not follow withdrawal periods—which refer to the minimum period of time from administering the last dose of antibiotics and the production of meat for food. The purpose of following withdrawal periods is to ensure that foods do not contain residues of antibiotics in excess of the designated safe tolerance limit of that particular antibiotic. No prescription was required to buy feed mixed with AGPs as well as feed premixed with antibiotics. Veterinarians were generally liberal with prescribing antibiotics which is believed to be influenced by incentives from pharmaceutical companies. Bigger farmers, despite being more aware and resourceful than smaller farmers, were also not practicing good farm management measures. To attain favorable FCR, farms heavily relied on antibiotics. Use of antibiotics was considered an easy and the most economical solution for high profitability.

Apart from CSE's study, there are many other studies that have reiterated the presence of antibiotic resistance determinants—residues, bacteria and genes—in chicken meat samples collected from various locations in India, which is attributed to antibiotic use in this sector. For example, isolates of *E coli* resistant to ampicillin, gentamicin, ciprofloxacin, nitrofurantoin, co-trimoxazole, tetracycline, cefuroxime, imipenem, nalidixic acid, chloramphenicol, and ceftriaxone were reported in chickens grown for both meat and eggs in farms in a multi-institutional study done in Punjab in 2017. In another study, researchers from the Christian Medical College, Vellore and the Apollo Cancer Institute, Chennai, reported the presence of colistin resistant determinants—resistant bacteria, *MCR* genes and mobile genetic elements—in retail food samples such as meat, vegetables and fruits sold in Chennai in 2018.

Bacterial isolates of *Salmonella* spp resistant to tetracycline, erythromycin, nalidixic acid, ampicillin and ciprofloxacin have also been reported in chicken samples from Uttarakhand and Uttar Pradesh in a 2019 study published by researchers at the G B Pant University of Agriculture and Technology, Uttarakhand. That same year, isolates of *Salmonella* spp resistant to tetracycline, gentamicin, chloramphenicol, azithromycin, erythromycin, nitrofurantoin, trimethoprim, and amoxillin were found in chicken liver meat and egg samples collected from Mumbai. The study was done by the National Facility for Biopharmaceuticals, Mumbai.

The net of antibiotics

A leading fish producing state, West Bengal, rears inland fish in freshwater and brackishwater farms. Field visits by CSE researchers show that the use of antibiotics is high in intensive farming



Sources: Handbook on Fisheries Statistics 2014 (Ministry of Agriculture); Handbook of Fisheries Statistics 2014-15 (Government of West Bengal), State of the World Fisheries and Aquaculture, 2016 (FAO)



What CSE found

Of 22 fish farms/ hatcheries, 7 admitted to using antibiotics. Six out of the seven were semi-intensive/ intensive farms

3 farms/ hatcheries denied using antibiotics, but CSE found evidence of antibiotics at the site

10 farms/ hatcheries denied using antibiotics. Six of these were traditional farms. CSE did not see any evidence of antibiotic use

2 farms/ hatcheries did not allow CSE to enter the premises

Purba Medinipur, which has mostly intensive farms, saw highest cases of people admitting to antibiotic use, while North 24 Parganas, which saw the lowest, has mostly traditional farms

Antibiotics in aquaculture

In 2016, a CSE study found rampant use of antibiotics by the aquaculture sector in West Bengal, which is a leading fish producing state. CSE visited 22 traditional, semi-intensive, intensive freshwater and brackish-water farms. They also visited hatcheries and had discussions with farmers and farm owners. Information was also gathered from representatives of stakeholder government departments—both Central as well states—pharmacists and feed suppliers. The study found that antibiotics were being used across freshwater farms, brackish-water farms as well as hatcheries. Antibiotics—such as oxytetracycline, tetracycline, enrofloxacin, ciprofloxacin, norfloxacin, ampicillin, dicloxacillin, amoxicillin, azithromycin, cephalexin, streptomycin and kanamycin—were routinely used for mass disease prevention and maintaining a high productivity rate (see "The net of antibiotics").

Several other issues came to light. For example, availability of antibiotics for aquaculture was largely unregulated, and antibiotics were easily available over-the-counter (OTC), including those which are critically important for humans. Farmers were also using antibiotics meant for poultry or livestock, but not for fish. Recommendations on withdrawal periods too were not being followed. Typically, fishery officers were not authorised to prescribe medicines. Therefore, farmers relied largely on peers, quacks, company representatives or self-discretion to use antibiotics. There were also inconsistencies in recommending antibiotic use in handbooks and pamphlets circulated during training at district fisheries offices. Quacks are also believed to have tie-ups with pharmacists leading to overuse.

Aligned with the findings from CSE study, other studies too have reported the presence of antibiotic resistance determinants in fish meat and aquaculture products from India and attributed it to antibiotic use in this sector. For example, in 2005, researchers at the College of

Fisheries, Mangalore, reported the presence of *E coli* bacterial isolates that were resistant to ampicillin, nalidixic acid and cephalothin from seafood samples collected from fish markets and seafood processing plants in and around Mangalore.

In 2012, residues of chloramphenicol, sulfonamides and erythromycin were found in farmed shrimps collected from Andhra Pradesh, Tamil Nadu, Karnataka and Kerala. This study was jointly done by the Export Inspection Agency, Kolkata, and the Central Institute of Fisheries Technology, Kochi. In 2017, researchers at the Central Institute of Fisheries Education in Mumbai found *Enterobacteria* spp isolates resistant to cefotaxime, ceftazidime, cefpodoxime, aztreonam, ertapenem, meropenem in fish, shrimps, clam, squid that were being sold in Maharashtra. Isolates of *Aeromonas* spp bacteria resistant to ampicillin, cephoxitin and carbenicillin were isolated from fish collected from local retail outlets in Mumbai in 2011 by researchers at the Bhabha Atomic Research Centre, Mumbai.

Antibiotics in fast food

In 2017, CSE highlighted the double standards of the fast food industry towards addressing antibiotic use in their meat supply chains. It was found that fast food multinational companies such as McDonald's, KFC and Pizza Hut do not have any India-specific commitments to eliminate misuse of antibiotics in their meat supply chains though these companies have made ambitious, specific and time-bound commitments in the US and other countries owing to growing pressure from investors and consumers.

To understand India-specific policies and commitments to reduce or eliminate antibiotic use in meat supply chains of the fast food companies, CSE sent a questionnaire to 12 companies selling fast food and managing 14 key brands. These include nine companies operating 11 multinational brands. The remaining brands are managed by three Indian companies. Five companies (operating six brands) responded to CSE's queries. But none of these companies shared an India-specific time-bound commitment to reduce or eliminate antibiotics in their supply chains.

Antibiotics in dairy sector

Research organisations, other than CSE, have carried out many studies over long periods of time to report the extent to which antibiotics are used in the dairy sector, where they are used for preventing diseases such as mastitis (infection of the udders). They too have found antibiotic residues in milk samples. For example, a multi-institutional study from Bihar conducted in 2014 reported isolates of *Salmonella* spp bacteria in milk samples that were resistant to antibiotics such as gentamicin, ampicillin, penicillin, and erythromycin. Bacterial isolates of ampicillin resistant *Listeria monocytogenes* have also been reported in milk samples from Varanasi. A 2015 study done by researchers at the Madras Veterinary College, Chennai, found antibiotic residues of enrofloxacin in milk samples collected from dairy farms in Tamil Nadu.

Availability of antibiotics for aquaculture are largely unregulated, and antibiotics are easily available over-the-counter, including those that are critically important for humans

In 2017, a joint study by Rajasthan University of Veterinary and Animal Sciences, Bikaner and Sawai Man Singh Medical College, Jaipur, found bacteria resistant to multiple antibiotics in milk samples from 13 districts of Rajasthan. Antibiotic residues of enrofloxacin, oxytetracycline, tetracycline, sulphamethoxazole were reported in milk samples collected from dairy farms and markets in Punjab in a study done by the Guru Angad Dev Veterinary and Animal Sciences University, Ludhiana, in 2019.

Regulatory journey

When CSE tested for antibiotics in honey in 2010, there were no standards for antibiotics in honey for domestic consumption. Standards that were prescribed—such as those of the Bureau of Indian Standards (BIS), Agricultural Produce Grading and Marking or AGMARK, and FSSAI—were only for honey composition and quality (like sucrose content, total reducing sugars and moisture content), but not for antibiotic residues.

However, in response to CSE's study and recommendations to develop standards for honey, the FSSAI set mandatory standards for antibiotics in honey in the Food Safety and Standards (contaminants, toxins and residues) Amendment Regulations in 2014. The standard provides tolerance limits for 10 antibiotics in honey.

In 2014, when CSE tested for antibiotics in chicken meat, there were still no standards for antibiotic residues in food products such as meat and eggs. The use of antibiotics in feed was largely unregulated. A national level surveillance system to monitor antibiotic resistance or antibiotic use in the food-animal sector was missing. There was no mandatory provision for farm hygiene and sanitation as well. Moreover, there were no effective framework targeted neither involving farmers or veterinarians to reduce the use of antibiotics. Similarly, in the case of the aquaculture sector, a comprehensive regulatory framework for freshwater culture was missing as the guidelines for coastal aquaculture focused largely on export-oriented brackish water culture. There were BIS fish feed standards for carp, catfish, marine shrimp and freshwater prawn, which prohibited a limited set of antibiotics in the fish feed manufacturing units, but these were voluntary in nature.

However, changes were observed since 2014. In December 2014, the Department of Animal Husbandry, Dairying and Fisheries (now Department of Animal Husbandry and Dairying) issued an advisory to all states to not allow antibiotics in feed and feed supplements as growth promoters. The advisory also outlined the need to ensure that the use of antibiotics must be based on veterinary prescription and under veterinary supervision. It also said that alternatives such as antibiotic-free growth promoters should be encouraged, and systems must be put in place to trace antibiotic residues from manufacturer to user and to ensure sale of licensed antibiotics through registered distributors. In 2018, FSSAI notified tolerance limits for 103 antibiotics and veterinary drugs in edible animal tissues and fat derived from animals, fish, eggs and milk.

103

The number of antibiotics and veterinary drugs that the FSSAI has notified tolerance limits for residues

In 2019, the Ministry of Health and Family Welfare banned the manufacture, sale and distribution of colistin and its formulations for food producing animals, poultry, aqua farming and animal feed supplements. The notification also says manufacturers of colistin and its formulations should label the container of the drug and mention the words "Not to be used in food producing animals, poultry, aqua farming and animal feed supplements" on the package insert and promotional literature.



Antibiotic administration starts well before the lifecycle of a broiler chicken in poultry farms

Taking a cue from the ban on colistin, the FSSAI drafted the Food Safety and Standards (Contaminants, Toxins and Residues) Amendment Regulations, 2019, which does not permit the use of colistin. Tolerance limits for colistin will therefore be removed from the FSSAI list of antibiotics and veterinary drugs for food, and added to the list of drugs prohibited for use in processing of meat and meat products, poultry and eggs and sea foods, including shrimps, prawns or fish and fishery products.

State governments too are waking up. In 2016, the Andhra Pradesh government acknowledged the learnings from CSE's study on aquaculture and constituted district and taskforce committees to check for antibiotic misuse in this sector. The Coastal Aquaculture Authority (CAA) has also been registering antibiotic-free aquaculture inputs and shrimp hatchery operators, and farmers have been directed to use only registered antibiotic-free aquaculture inputs.

The food industry too took some steps. In 2017, Jubilant FoodWorks Ltd, which has the franchise for Domino's Pizza and Dunkin' Donuts, announced a policy on "Usage of antibiotics in poultry bird's health management". The policy focused on eliminating antibiotic misuse in the chicken supply chain in a phased manner. It also committed to eliminate non-therapeutic use of antibiotics by 2018 as well as use of highest-priority critically important antimicrobials by 2019.



Fishery officials are not authorised to prescribe antibiotics

Roadmap to curb misuse

But much more needs to be done. Antibiotic misuse in food-animal production should be eliminated and this should include banning or phasing-out non-therapeutic use of antibiotics in animals. To ensure antibiotics are not used routinely for non-therapeutic purposes, a mechanism should be evolved and enforced so that they are used only in case of disease treatment, and that too based on the prescription of veterinarians. Towards this, the development, production and use of antibiotic-free growth promoters such as herbal supplements could be explored. Further, antibiotics that are critically important for humans should not be allowed for any use in animals, including for therapeutic use.

The government should also formulate standards for animal feed and regulate the business. Medically important antibiotics that are important for human health should not be allowed for use in feed and feed supplements. Despite efforts, feed—which is an important route for administering antibiotics to food-animals for non-therapeutic purposes such as for growth promotion and disease prevention—is not regulated. Feed containing antibiotics continue to be sold in the open and online markets. The Poultry Feed Standards of the Bureau of Indian Standards, 2007, mention that antibiotics with systemic action should not be used as growth promoters in feed, but these standards are

voluntary in nature and cannot be enforced. There have been limited discussions in the poultry feed committee of the BIS over the last few years, but no concrete outcome has been achieved yet. In aquaculture, just like in case of poultry, the BIS should amend fish feed standards to mandatorily prohibit antibiotic use in feed.

Moreover, instead of depending on antibiotics, the country needs to ensure good farm and waste management practices to control infection and stress among the flock. Biosecurity guidelines should be improved and enforced. Capacity of small farmers must be enhanced so that they can comply with the guidelines. The guidelines should be legally enforced on big companies. The use of alternatives such as prebiotics or probiotics, vaccinations against bacterial diseases, improved water quality in farms should be encouraged to bring down the risk of bacterial infection and unnecessary antibiotic use. Veterinarians should be educated and trained on the judicious use of antibiotics and infection prevention.

To achieve this, a clear-cut plan or a roadmap is the need of the hour, which should be supported by necessary government policies, programmes, training and funding. This could include government programmes on raising farmer awareness about the impacts of antibiotic misuse in animals, programmes to ensure improved availability of low-cost disease diagnostic kits or alternatives such as prebiotics or probiotics to farmers, training of farmer to adopt better farming practices.

A surveillance system to monitor all AMR causing determinants—resistant bacteria, antibiotic residues and resistance conferring genes should be developed for food-animals and food. This will help generate data for better formulation of policies and decision making. This should be further integrated with those in other sectors such as human health or environment in the interest of harmonisation. In addition to the ongoing monitoring of antibiotic residues in food, FSSAI should develop a comprehensive framework to monitor resistant bacteria as well. Additionally, monitoring the usage of antibiotics at various levels such as producer, seller or user should also be carried out. Efforts should be aimed to estimate antibiotic usage in different food sectors such as poultry, dairy, aquaculture and crops or its use for therapeutic or non-therapeutic purposes. To facilitate monitoring, there should be a mechanism to ensure that only a licensed antibiotic should reach the registered user through a registered distributor or stockist of veterinary medicines. All animal antibiotics should be traceable from the manufacturing site to user and a stringent control on the import of antibiotics and feed supplements should be implemented. Surveillance data should be collated into a national-level surveillance database and placed in the public domain.

The government should also formulate specific rules for specific sectors. A separate regulatory framework for freshwater aquaculture should be developed on the lines of CAA, which regulates coastal (brackish water) aquaculture. A national-level programme for issuing "Pond Health Cards" should be initiated by the department of fisheries. For fishery professionals, a fisheries council should be created to ensure professional disease

Recommendations made by CSE in its various studies have been recognised and accepted as part of India's National Action Plan on AMR, for which CSE is also a key implementation partner



The fast food industry adopts double standards while addressing antibiotic use in their food production supply chains

management and authorisation of fishery science professionals to prescribe medicines. Here too, the unregulated availability of antibiotics needs to be checked by the Central Drugs Standard Control Organization (CDSCO). The state drug departments should ensure that approved antibiotics, suitably labelled for use in fish, are sold only with a prescription. CDSCO should develop and implement an online system to track the sale and distribution of antibiotics.

The Indian fast food industry has an important role to play. Companies managing both Indian and foreign multinational brands must come forward and contribute to halt rising AMR. Fast food companies must make time-bound and aggressive India-specific commitments to eliminate or phase-out antibiotic use in their supply chains. These commitments must aim to eliminate all non-therapeutic use of antibiotics and clearly indicate by when the company plans to eliminate antibiotic use as a growth promoter as well as antibiotic use in disease prevention. The companies must also commit not to use any medically important antibiotics altogether in the long-term. Moreover, the commitments should aim to include products from all food-animals (chicken or fish) relevant to a company and specify accordingly. To achieve the commitments and share the status of progress, third-party supply chain audits, laboratory testing for antibiotic residues and resistant bacteria and documentation of antibiotic use should be made an integral part of the process. Such commitments, audit reports or test reports should be put up in

public domain. Going forward, a mechanism by which consumers are informed about the way in which animals reared for meat they are consuming has been grown (with or without routine use of antibiotics) could be considered. This would also incentivise the farmer who can charge a premium and provide consumers with a healthy choice.

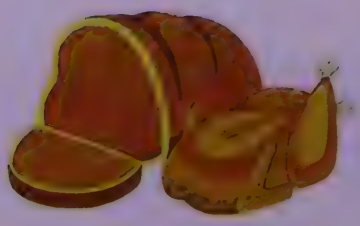
India is one of largest producers of meat and milk globally, which not only has a high domestic consumption, but is also exported. Due to increasing population and growing demand for cheap protein such as meat, milk and eggs, food production systems are adopting intensive farming approaches that involve high stocking density and use of chemical inputs. To contain AMR, it is important that such food production systems make a transition to sustainable settings with reduced dependence on chemicals such as antibiotics, and better farm and waste management practices.

India's National Action Plan (NAP) on AMR recognises AMR as a One-Health issue and provides a comprehensive and multi-sectoral approach to address AMR. Further, the Delhi Declaration also indicates political commitment at the highest levels. Therefore, effective implementation of NAP is the key to successfully containing AMR across all sectors. Recommendations made by CSE in its various studies have been recognised and accepted as part of India's NAP-AMR, for which CSE is also a key implementation partner.

The NAP also calls upon states to establish AMR as a state level priority and ensure its implementation on the ground. Moreover, with health, animal husbandry and agriculture being state subjects, the role of state governments is even more important. More states should come forward and develop state-level action plans that take into consideration different ground realities, challenges and specific interventions. For example, a state like Andhra Pradesh, with high poultry or fishery production, or Haryana and Madhya Pradesh, which are high milk producers, should focus to reduce antibiotic misuse in the food-animal sector. For states like Delhi, which have a high population density, managing waste (sewage) in view of AMR will be an area of concern. At the same time, states should move forward and develop policy instruments, systems and tools specific to containing AMR, instead of waiting for the Union government to make the first move. There is also a greater need for awareness and capacity building efforts at the state level. Necessary budgetary allocations at the Centre and at the state will also be crucial for the timely implementation of NAP. CSE has also worked with states such as Kerala, Madhya Pradesh and Delhi to help develop as well as implement respective state action plans on AMR.

Unexpected exposure

BHAVYA KHULLAR lists common foods that could be contaminated with antibiotics



3

MEAT SUCH AS CHICKEN AND PORK

CSE found antibiotic residues of tetracyclines, ciprofloxacin and enrofloxacin in chicken meat samples collected from Delhi NCR in 2014. In 2019 *Staphylococcus aureus* isolates resistant to cefoxitin and oxacillin were found in pork samples collected from retail meat shops in Assam.



2

HONEY

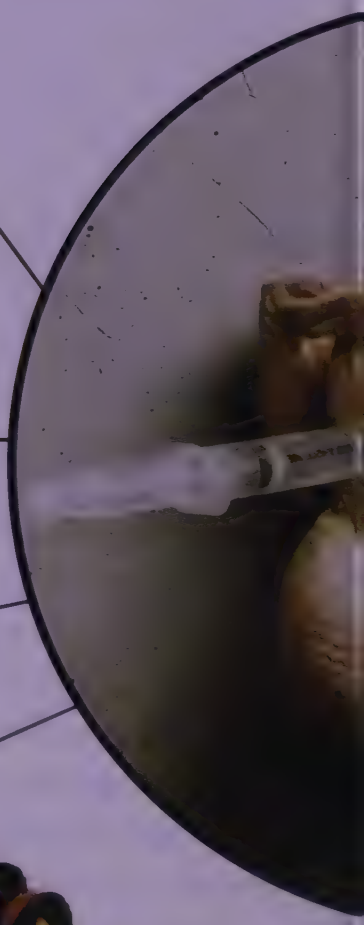
Antibiotics such as tetracycline are mixed with sugar and left on bee boxes for bees to feed on. This prevents diseases in bees. In 2010, CSE tested 12 brands of honey and found residues of antibiotics such as oxytetracycline, erythromycin, chloramphenicol, ampicilin, enrofloxacin and ciprofloxacin in samples.



1

MILK

Antibiotics used in dairy animals make their way to their milk and milk products like cheese. When FSSAI tested 6,432 milk samples from across the country in 2018, 77 samples had antibiotic residues above permissible limits. According to a study in 2017, milk samples from Rajasthan had *Staphylococcus aureus* resistant to tetracycline and gentamycin.

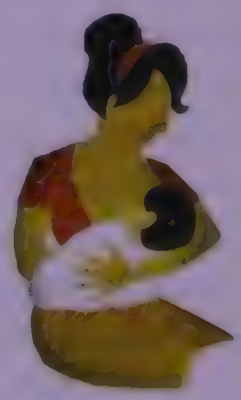




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SPROUTS

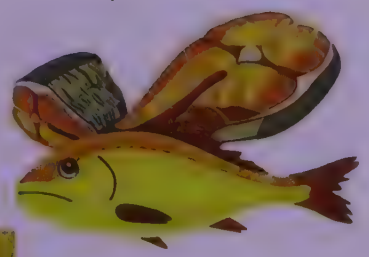
Ready to eat *mung* sprout samples picked up in Mumbai were tested for the presence of antibiotic resistant bacteria and resistant *Acinetobacter* spp, *Enterobacter* spp and *Klebsiella* spp were isolated.



9

BREAST MILK

The Human Milk Artificial Pollutants (HUMAP) study done by researchers in Turkey in 2018 was the first to report that antibiotics such as beta lactams and quinolones could be present in human milk samples. This happened even though the mothers did not receive these antibiotics during pregnancy and lactation.



4

FISH AND AQUACULTURE PRODUCTS

Antibiotics are used extensively in aquaculture. In 2017, researchers at the Central Institute of Fisheries Education in Mumbai reported the presence of *Enterobacteria* spp resistant to cefotaxime, ceftazidime, cefpodoxime, aztreonam, ertapenem, meropenem in fish, shrimps, clam, squid being sold in Maharashtra.



5

EGGS

When egg-laying hens are given antibiotics for non-therapeutic purposes, the residues can make their way to the eggs. Residues of chlortetracycline were found in eggs collected from farms in Namakkal, Tamil Nadu in 2014.





6

FRUITS AND VEGETABLES

Antibiotic residues have been reported in crop products such as fruits and vegetables (under laboratory conditions) in the US. Small quantities of streptomycin residues were detected in apples on which this antibiotic was sprayed. There are no studies on antibiotic residues in crops from India but antibiotics are used widely in agriculture here too.



7

BABY FOODS AND FORMULA MILK

Residues of chloramphenicol and sulphamethazine were found in baby foods and formula milk of popular brands such as Dexolac, Nestogen and Cerelac collected from Delhi in a study published in 2017.



8

DRINKING WATER

Bottled water samples of 30 brands, collected from six states of India had bacteria resistant to ampicillin, nalidixic acid, novobiocin and oxytetracycline.

GROWING RESISTANCE

Indiscriminate use of antibiotics on food crops could add to the burden of antibiotic resistance

BHAVYA KHULLAR, RAJESHWARI SINHA, AMIT KHURANA

DHARAMPAL SINGH just cannot stop admiring the cauliflowers glistening with beads of dew in his farm on the banks of Yamuna in Delhi. Next to the plot, rows of radishes, spinach, fenugreek and bottle gourds lie shining in the morning sun. "These untainted vegetables fetch me a premium in the market," says Singh, as he prepares to spray a white powder on the crop. "Spraying this at regular intervals ensures that my plants stay healthy and green until harvest." The powder, which Singh has been using so generously for last few decades, is streptocycline—a mixture of two antibiotics used for treating life-threatening bacterial infections in humans. In fact, the World Health Organization (WHO) recognises the antibiotics—streptomycin and tetracycline—as "critically" and "highly" important for humans.

Streptomycin is used in humans for "previously treated tuberculosis" that accounts for over 10 per cent of the estimated 2.7 million TB incidences in India. It is also used to treat multidrug-resistant TB and certain cases of TB meningitis. Resistance to streptomycin is already high and its large-scale non-human use could add to the problem. Doxycycline—belonging to a class of tetracycline—is the drug of choice for treating rickettsial diseases. It gets transmitted by insects and is a covert re-emerging infection in India.

Extent of use

The indiscriminate use of such crucial antibiotics is worrying as the practice may lead to the development and spread of antimicrobial resistance (AMR), already a pressing concern worldwide; at least 10 million people are likely to die of AMR every year by 2050. When used in crops, unspent antibiotics find their way into the surrounding environment.

Microorganisms exposed to this increasing load of antibiotics in soil and water can develop resistance to it. The resistance can spread to other bacteria through transfer of genetic material. When humans or animals get infected by such resistant microorganisms, their treatment becomes difficult as well as expensive. It is possible traces of antibiotics remain in edible parts of the plant long after streptocycline is sprayed, affecting human health or making them antibiotic-resistant.

To gauge the extent of the use of antibiotics on crops in the country, researchers at New Delhi-based Centre for Science and Environment (CSE) visited several farms near the banks of the Yamuna in Delhi as well as in Fazilka district of Punjab and Hisar district of Haryana. They also spoke to fruit growers in Maharashtra, Andhra Pradesh and Himachal Pradesh. Just like Singh, none of the farmers knew that streptocycline is a combination of antibiotics, and were routinely using it as any other pesticide.

The Central Insecticide Board and Registration Committee (CIBRC), the country's apex body that approves the use of pesticides, says streptocycline should be used when plants develop bacterial infections like leaf blight, fire blight, citrus canker, rotting of fruits and stems, leaf



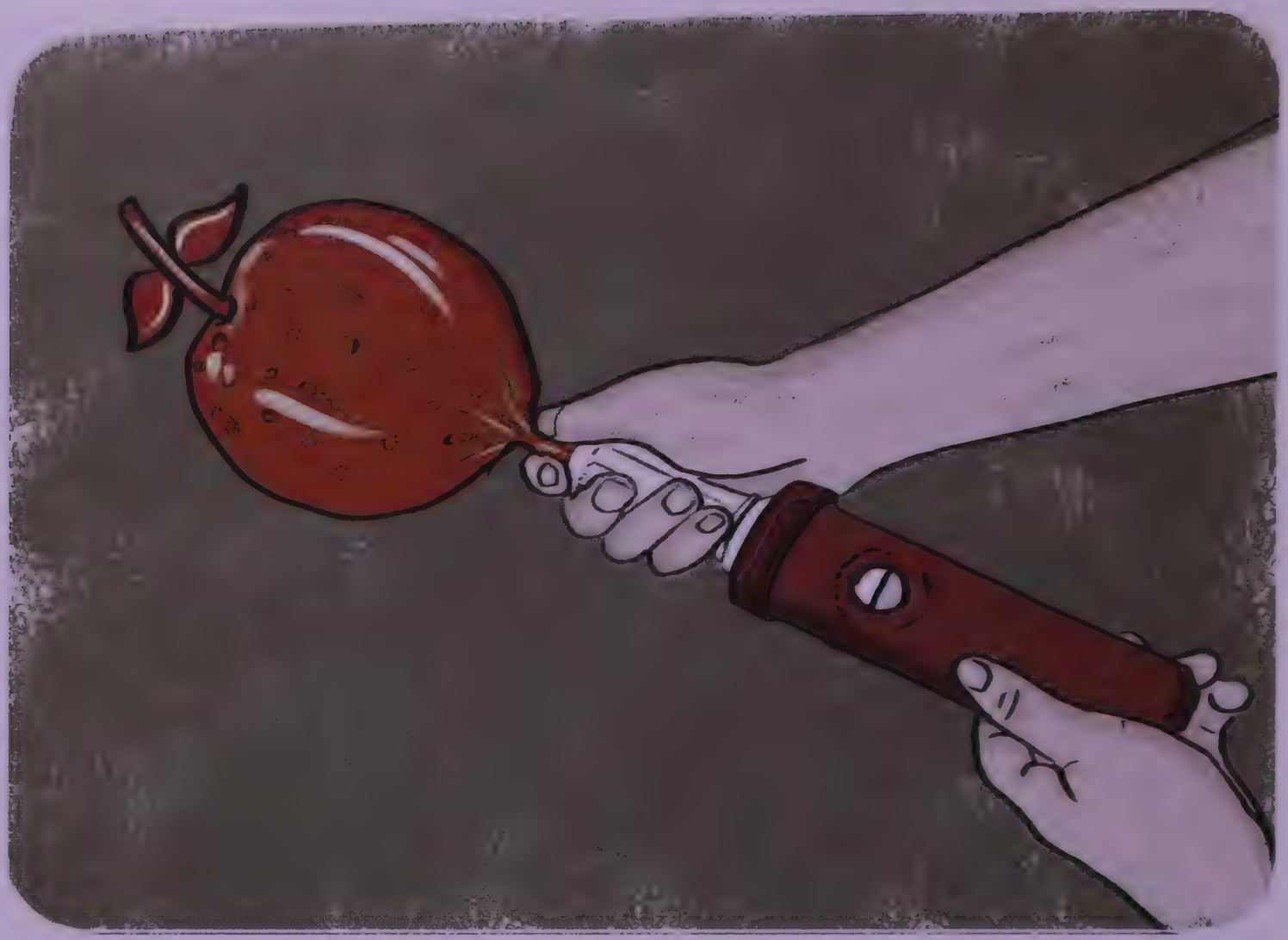
spots and soft rots (yellowing and drooping of leaves).

But CSE researchers found the farmers using it even in the absence of disease symptoms. Worse, there is little monitoring on how it is being applied. "We use streptocycline to avoid infections and subsequent crop loss," says Satpal, a vegetable grower in Delhi. He mixes streptocycline with a host of other medicines and sprays on the plants twice a week throughout the crop season. "This way plants do not contract *jhulsa rog* (yellowing or drying)," he says.

In Hisar, vegetable grower Ram Avtar Saini vouches by the efficacy of streptocycline: "It's the only medicine that can save bottle gourd from *galav rog* (rot)." In the first week of November, when CSE spoke to him, he had procured 30 packets of streptocycline, each weighing 6 grammes (g). CSE also found that farmers were using streptocycline with little regard to the recommendations by CIBRC. For instance, CIBRC recommends using streptocycline only on two fruits—apple and citrus. But in Maharashtra's Akola district, Rahul Asbe says he has already sprayed streptoycline five times on his pomegranate crop: "Two more rounds will be done before the harvest in December."

Farmers in the Yamuna bank admit to be routinely using streptocycline on cauliflower, cabbage, spinach, bottle gourd, apple gourd, cucumber, mustard, brinjal, fenugreek, radish and coriander, whereas CIBRC recommends its use on beans, potatoes and tomatoes.

There are also grave anomalies in the way streptocycline is being used. Most farmers say they mix fungicides with streptocycline before spraying as they are unable to distinguish fungal or bacterial diseases. "Modes of action of antibiotics and fungicides are different, and there is no evidence to suggest that



streptocycline enhances the action of other chemicals," says Dinesh Singh, principal scientist at the Indian Agricultural Research Institute (IARI), New Delhi. CIBRC recommends specific dosages of streptocycline for different crops. For example, a solution of 25-50 parts per million (ppm) is recommended for apples in case of fire blight; 100-150 ppm for beans with halo blight; and 40-100 ppm for tomatoes with bacterial leaf spots. But farmers rarely follow the recommendations. CSE researchers found that farmers usually dissolve an entire packet of streptocycline in different volumes of water, depending on the capacity of the tank of the air-blast sprayer with them. The resulting concentration is three to four times higher than what is recommended.

To understand the reason for such routine violation of CIBRC recommendations, CSE looked at a few state agriculture institutes that run Krishi Vigyan Kendras (KVK) to help farmers tackle agriculture-related problems. A glance at their websites shows many KVKs recommend streptocycline on crops not listed for use by CIBRC. Explaining the reason, a senior official with the Dr Y S R Horticultural University at Tadepalligudem, Andhra Pradesh, says: "University recommendations are based on guidelines of the Indian Council of Agricultural Research (ICAR). These may be different from CIBRC but are based on scientific evidence." Another scientist at the Dr Y S Parmar University of Horticulture and Forestry at Nauni, Himachal Pradesh, says KVK recommendations are based on scientific studies and regional or local requirements. "If blight appears on pomegranate, streptocycline will have to be used despite CIBRC not recommending it," he adds.

Lack of guidance

But CSE researchers' discussions with farmers show otherwise. In the absence of a robust extension machinery, the farmers' actions appear to be influenced by what pesticide dealers say. "I do what Shyam suggests," says

Ram Avtar, referring to the local pesticide dealer. "We have not met any government official in years. Shyam and company doctors (representatives selling streptocycline) are the only help we have," he adds. In Fazilka, Vinod Kumar, who grows orange, lemon and kinnow on his 12 hectare farm, also cites lack of support from extension officers as a reason for seeking guidance from pesticide dealers. When CSE contacted pesticide dealers, they said they prescribe dosages as recommended by companies or the government. "But only 10 per cent of the farmers give the right dose," says Arvind Kumar Patel, secretary of the Agro-Input Dealers Association, Pune.

Commenting on the effectiveness of the extension machinery, Beant Singh, chief agricultural officer of Fazilka, says: "There is a provision to fine and punish those who violate norms and sell unapproved chemical inputs. Agriculture officers regularly inspect pesticide shops to prevent such sale." However, a senior official with Maharashtra's state agriculture department in Amravati admits that lack of staff and added responsibilities are reasons for weak enforcement on the ground. "Existing insecticide officers are assigned multiple tasks on issues of soil and water, natural calamities and sometimes even insurance-related matters. There is not enough time for effective enforcement on the ground," he says.

Surprisingly, key drug regulator of the country, the Central Drugs Standard Control Organisation (CDSCO), does not have any role in regulating antibiotics used on crops. Highlighting the definition of "drug" as stated in the Drugs and Cosmetics Act (D&C Act), 1940, a senior CDSCO official says, "Antibiotics meant for plants or crops do not fall within the purview of the present drug laws. Hence, CDSCO has no jurisdiction over antibiotics sold for treating plant diseases."

When asked about the role of state drug regulatory bodies, a senior official at the Food and Drugs Control Administration in Gujarat says, "State drug authority cannot exercise any control over companies that manufacture or sell antibiotics for use in crops as they manufacture and sell the product as pesticides."

To add to the above, CIBRC has wrongly registered streptocycline as a fungicide. When enquired, a CIBRC official on condition of anonymity, said: "The classification depends on what companies mention on their application forms and the supporting data they submit during registration. Unless this is challenged with data, CIBRC cannot reclassify the chemicals into a new category." The justification seems weak as companies should align their actions with laws set by regulatory authorities and not vice versa. CIBRC also does not provide any withdrawal period for antibiotics, which ensures that chances of antibiotic residues present in food are reduced.

To make matters worse, streptocycline is assigned low toxicity, meaning no special precaution needs to be taken for its use. But this labelling does not consider health hazards like AMR which could arise due to exposure of farmers to the antibiotics they spray.

Laboratory-based studies have also shown the presence of antibiotic residues in crops at a later stage. But the Food Safety and Standards Authority of Indian (FSSAI) does not provide any separate tolerance limit for streptocycline in food products. A national record of antibiotics being produced or consumed as pesticides for crops is also lacking.

Ironically, when CSE had filed an application under Right to Information with the Directorate of Plant Protection,

Antibiotics are meant to treat bacterial diseases in humans and should not be used as pesticides. It should be used under expert supervision only after a disease has been detected in a crop

The government should strengthen the extension machinery and carry out surveillance of antibiotic use in crops

Quarantine and Storage (PPQS) to enquire about annual consumption of streptocycline used for crops, it disposed of the request in May 2018, saying it does not have the information. Though the data was made available on its website a few months later, its veracity is doubtful. For instance, total consumption of streptocycline in the country during the two years between 2014 and 2016 is 0.21 tonnes, while it is 25 tonnes for 2016-17 alone. Data available on the website of Hindustan Antibiotics Ltd (HAL), which manufactures brand "Streptocycline" in India, shows it has capacity to produce 18 million packages of 6 g each. This means it can produce 108 tonnes of streptocycline a year. Even if 50 per cent of it is used in India, consumption would be close to 50 tonnes. CSE researchers found other brands of streptocycline being sold, such as unimycin, tagmycin, streptosac, agromycin and cristocyclin.

The presence of residual antibiotics in the environment after their spraying on crops and their linkages to AMR remains a matter of concern across countries where antibiotics are used on crops. But some have found ways to regulate its use. For instance, streptomycin and oxytetracycline (which belongs to the class of tetracycline) are not approved for use in the European Union.

These are allowed to be used only under exceptional circumstances, such as in case of a disease outbreak that cannot be contained by other means. A recently released report by the Food and Agriculture Organization and WHO recognises the link between antimicrobials used in crops and AMR. The report recommends integrated pest management as an effective approach to limit the use of antimicrobials in crops.

Tackling the problem

Pesticides are agro-chemicals used to protect plants from pest attacks. Antibiotics, on the other hand, are drugs meant for treatment of bacterial diseases in humans. They should not be used as pesticides and be used under expert supervision only after a bacterial disease has been diagnosed in a crop. All other uses of antibiotics should be considered as misuse and phased out. To contain AMR from the agriculture sector, multiple stakeholders should take urgent steps.

CDSCO needs to consider amending the D&C Act to bring antibiotics used in plants as "drugs" under its purview. Necessary law, such as Schedule H for antibiotics, should be introduced to ensure that no antibiotic is sold for use in agriculture without prescription. CIBRC should reclassify streptocycline as an antibiotic and ensure that it is not sold as fungicide or pesticide. It should also set withdrawal periods for streptocycline, and revisit its toxicity labelling considering AMR.

The Ministry of Agriculture and Farmer's Welfare (MoAFW) should work towards strengthening the extension machinery and creating awareness among farmers, dealers and extension officers towards limiting antibiotic misuse in crops. Just like antibiotics are prescribed for humans and animals, MoAFW should introduce the concept of "plant health experts" and train them to help farmers with disease diagnosis and use of inputs.

Alongside, ICAR should engage in research and development of effective and low-cost alternatives to antibiotics. PPQS should carry out surveillance of antibiotic used in crops and make data available in the public domain. FSSAI should come out with separate tolerance limits for streptocycline in food and conduct surveillance for monitoring antibiotic residues in plant-derived food.

इसरो ISRO

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SAFER OPTIONS TO ANTIBIOTICS

Many alternatives to antibiotics have cropped up to help the food industry fight diseases caused by bacteria in animals

SUDHI R

ALONG WITH humans making and consuming antibiotics, the other contributors of antibiotic resistance are agriculture, fishery and livestock farming. The amount of antibiotics used in the farm animal food industry is three to four times more than those used by humans in many developed and developing countries. This is seen as essential to ensure food security.

However, there are ways to reduce the use of antibiotics in the food industry. There are many prophylactic methods such as the use of vaccines. These are widespread in the poultry industry and nearly 95-100 per cent of poultry is vaccinated against many diseases, except in backyard systems. Others options like the use of immunomodulators helps improve the animals defence mechanism so that the animals does not succumb to diseases. For this, formulations containing, zinc, selenium, chromium, vitamin E, and products containing bacterial cell wall lipopolysacharides are being marketed widely in India.

Managing the chicks' stress too helps and this can be done just by simple things like providing clean air through forced ventilation in farms or assuring availability of clean sanitised drinking water round the clock. Herbal stress relieving formulas, herbal liver supplements, cool hour feeding programme for tropical climate can also prevent stress. Promoting the breeding of indigenous breeds which are geo-climatically adapted is also an alternative. The chicks' health can be improved by adding organic acids such as acetic acid (vinegar) and formic acids to feed and water. This helps in improving digestion as well in controlling pathogenic organisms.

A number of commercial acidifiers are quite successful and they have already replaced AGP (antibiotic growth promoter) mixed feeds in the European Union and countries that have banned antibiotics in poultry. To minimise the presence of toxins in the feed, toxin binders like activated carbon and bentonite are added to the feed. Almost all poultry feeds marketed in India are adding toxin binders according to seasons.

Remedies at hand

Extracts from turmeric, ginger, pepper and garlic are effective antimicrobials and can be added to the feed to control bacteria. Enzymes from genetically engineered colonies of microorganisms and bacteriophages which can enzymatically break down the cell wall of the specific bacteria, or hinder with DNA transcription or protein synthesis of bacteria too are being used. Earlier, enzymes like cellulase and phytase were used for better



digestion and health; but now the enzymatic treatment is the emerging trend in India.

The other method to reduce the use of antibiotics is to improve biosecurity and ensure that harmful pathogenic organisms are not present at the farm. Infrastructure which prevents the entry of pathogens, vectors, vermin or predators into the farming system must be encouraged. Environment control houses with high level of automation and sensors for temperature, humidity, carbon dioxide and ammonia load are already in practice all over the world. These are now quite common in India. The capital invested can be recovered in a matter of two years and this will increase profits by 10-20 per cent annually.

The capital cost of automation from the gold standard company would be around `400 per bird, and cost of construction with insulated sandwich panels is around `600 per bird. The government should promote this system by making it mandatory and also by providing soft loans and interest subsidies on prompt repayment. However, the ground reality is that these technologies are being adopted by the Indian poultry industry mainly to prevent economic losses due to diseases and not because of antibiotic resistance which is evident from the practice of mixing antibiotics in feed as a prophylactic measure. But from my experience, I can say that these methods work very well to phase out chemo prophylactic use of antibiotics and withdraw antibiotics completely in some farms for the last 5-6 years, with even decreased incidence of disease and its threat.

Regulation for prudence

There is a need to improve policies. There must be formulation of international policies that regulate import and export of food and feed



and it must be strictly regulated for antibiotic usage. For example, instead of simply rejecting a product due to the presence of antibiotic residue, the whole lot of product must be seized and destroyed by the international agencies, otherwise it will be exported to some other countries which has less stringent norms or will be converted to some pet foods.

There should be a policy to reduce the use of antibiotics for growth promotion and as feed mixes for prophylactic purposes. Trade of antibiotics must be regularised for therapeutic purpose only with strict legalised medical prescription and supervision. State departments of animal husbandry must be strengthened and given powers and responsibility for adhering to the norms of food production and food safety.

State laboratories and infrastructure should be strengthened to ensure that the cause of mortality in animals is identified at the earliest and assistance must be given to farmers to treat the flock. There is a need to generate public awareness among people on antibiotic usage and how it is linked to health.

DISEASES INSIDE HOSPITALS

You may not be told. Infections that emanate from hospitals are increasing across India. What we need is clinical antibiotic stewardship, hand hygiene, surveillance and monitoring of antibiotic resistance

BANJOT KAUR



RADHIKA SINGH, 55, had a femur fracture around two years ago. She was admitted to a Delhi hospital for a surgery. As she was immobile for four days, a catheter was inserted to ensure that she did not have to be carried to the washroom all the time. After four days, the doctor wanted the catheter to be removed. Her son insisted he wanted the catheter to be used for some more days so she could get more rest. The doctor gave in and did not remove the catheter for three more days after which she was discharged. However, she returned to the hospital within a week with rashes on her hip. After a number of investigations, it was found that the rashes were not because of the surgery but due to the overuse of catheter. She developed device-associated infection, also termed as Hospital-Acquired Infections (HAI) or nosocomial infections. Resistant to antibiotics, the infection spread to Radhika's entire left leg because of which it had to be amputated.

HAIs are a challenge as they increase chances of antimicrobial resistance (AMR). Sarita Mohapatra, an assistant professor of microbiology at the All India Institute of Medical Sciences (AIIMS), New Delhi, says that a hospital environment offers a perfect setting for any pathogen to become resistant to antibiotics as patients are treated with a variety of these drugs. "As we try to put our best foot forward by using more and more antibiotics, the pathogen develops ways to fight these antibiotics," she says.

Such hospital-acquired antibiotic resistant infections came into prominence in India in 2009 when a 59-year-old Swede of Indian origin was admitted to a hospital in Örebro, Sweden after returning from India. While in India he developed an abscess in his buttocks and had been hospitalised, first in Ludhiana and later in Delhi where he was operated upon. In Sweden, he was admitted for treatment for bed sores and urinary tract infection. However, doctors found that antibiotics such as carbapenems—a class of antibiotics used for treating multi-drug-resistant infections—were not helping in treatment. A routine urine test revealed that the culprit *Klebsiella pneumoniae* had a gene—later named NDM-1 (New Delhi Metallo-beta-lactamase-1)—which made the patient resistant to almost all antibiotics.

Missing numbers

Very little data is available on antibiotic resistant hospital infections in India. At present, AIIMS, New Delhi, in collaboration with US-based Centers for Disease Control and Prevention (CDC) and the Indian Council of Medical Research (ICMR), has formed the HAI surveillance network which surveys more than 35 hospitals scattered across India with the help of more than 130 surveillance units. Preliminary data was collected between May 2017 and May 2019 in 50 healthcare centres across India. The survey analysed data for 0.75 million patient days. This included 0.23 million central line days, which indicate the number of days a patient is put on a central line in an Intensive Care Unit (ICU). These infections in medical parlance are known as device-associated healthcare associated infections (DA-HAIs). The number of blood stream infections due to central line were 4,630.

10

patients in every 100 contract hospital-acquired infections

So how do these equipments spawn infections? "Hospitals harbour millions of bacteria and whenever you insert a device like catheter or a ventilator, these bacteria get a chance to go into the bloodstream through the device. And, thus they are the perfect route for an infection," Mohapatra explains.

Amongst those patients who were affected by blood stream infections, 21.3 per cent were from medical/surgical ICUs. Worse, 14 days after the infections were identified, 37.5 per

Hospitals harbour millions of bacteria and whenever a device like a catheter or a ventilator is inserted, these bacteria get a chance to go into the bloodstream through the device. They are the perfect route for an infection

cent people died. By the end of this HAI surveillance network analysis, a little less than half of those contracted the infection (47.7 per cent) died. Most of the infections were caused by gram negative bacteria. *Acinetobacter* caused the maximum (24.6 per cent) infections. Acinetobacter"s resistance towards quinolone was 88.2 per cent and 92 per cent in case of 3rd generation cephalosporin.

A study carried out in Vardhman Mahavir Medical College and Safdarjung Hospital, Delhi—to determine the antimicrobial resistance of *E coli* isolates from the patients admitted in the ICU—showed that more than 90 per cent of the blood and 70 per cent of the faecal isolates were resistant to *cephalosporins*, a first generation antibiotic prescribed for Gram positive bacteria. On the other hand, 68 per cent of blood and 44 per cent of the fecal isolates produced the enzyme, extended spectrum betalactamase (ESBL), which made the antibiotics ineffective. The authors write in their paper, published in *Antimicrobial Resistance & Infection Control* in December 2018, that the antimicrobial resistant profile is alarming and poses a great threat to public health. They suggest that hospitals should urgently implement continuous surveillance and rational use of antibiotics along with effective hygienic measures.

Even babies are not safe from the scourge of antibiotic resistance in hospitals. They die due to failure of antibiotics against neonatal sepsis contracted in hospitals, says a study carried out by AIIMS researchers and published in the *British Medical Journal* in January 2019. The study estimates that 16 per 1,000 live births in India are infected with confirmed neonatal sepsis and one-third of them die for want of drugs that work. In this study, the babies acquired these infections from mothers who were subjected to unhygienic practices in labour rooms and neonatal intensive units of the hospitals.

These infections cost the patients dearly. A study by Center for Disease Dynamics, Economics & Policy to measure the burden of antibiotic resistance in India revealed that in-hospital mortality is significantly higher among patients infected with multidrug resistant (MDR) or extensively drug resistant (XDR) pathogens such as *Staphylococcus aureus, E coli, Klebsiella pneumoniae* and *Acinetobacter baumannii*. Researchers analysed antimicrobial susceptibility testing results and mortality outcomes of over 4,000 patients who visited one of the 10 tertiary or quaternary referral hospitals across India in 2015. The overall mortality rate among all study participants was 13.1 per cent, with mortality as high as 29 per cent among patients infected with *A baumannii*.

Researchers also found that among MDR infections, those caused by Gram-negative bacteria were associated with higher mortality rates compared to those caused by Gram-positive bacteria, with rates of 17.7 per cent and 10.8 per cent, respectively. The study also indicates that patients who acquired MDR bacterial infections were 1.57 times more likely to die, compared to patients with similar susceptible infections. Patients who acquired XDR infections were 2.65 times more likely to die. The findings were published on November 8, 2018 in *Clinical Infectious Diseases*.

Unclean hospitals

Hospitals in India are a hotbed of microbes just waiting to become resistant but the data is patchy. According to the Patient Safety Guidelines Framework 2018-2025, issued by the Union Health Ministry in May 2019, of every 100 hospitalised patients at any given time in developing countries, 10 people will acquire HAIs. This number is and seven in developed countries. The guidelines acknowledge that while institute-based systems for infection controls have been developed, there is a lack of integrated national level programme, policy or guidelines which cover healthcare institutions at all levels. It also accepts that there is no system of reporting HAIs at any level and there is no authority in place to collect, analyse and report HAIs at the country level.

The most quoted data on HAIs in India is from studies carried out in 2014 by the International Nosocomial Infection Control Consortium (INICC). INICC is an international medical non-profit founded by Victor Rosenthal, a microbiologist based in Argentina, and has a presence in over 50 countries. The INICC conducted a prospective surveillance study on surgical site infections in 10 hospitals in six Indian cities.

The study documented 1,189 surgical site infections (SSIs) which were associated with 28,340 surgical procedures. Breast surgery had the highest infection rate (8.3 per cent). Others included limb amputation (3 per cent), coronary bypass with chest and donor incision (4.3 per cent), cardiac surgery (6.5 per cent), craniotomy (3.3 per cent), herniorrhaphy (3.8 per cent), hip prosthesis (2.1 per cent), knee prosthesis (2.8 per cent), thoracic surgery (6.0 per cent), vaginal hysterectomy, (6.0 per cent) and exploratory abdominal surgery (4.0 per cent). Compared with the rate of surgical site infections (SSIs) as provided by US-based Centers for Disease Control and Prevention (CDC), the study found that SSI rates were significantly higher in 73 per cent of the surgeries whereas in 27 per cent, SSI rates were similar in this study and in the CDC-National Healthcare Safety Network report.

However, the study pointed out that while comparing CDC's hospital hospital infection rates with those of hospitals from Western Europe and Oceania, it is important to note that these countries have similar socioeconomic conditions. Therefore, it might not be correct to compare rates in the US with hospitals in countries with limited-resources or those without enough experience in the field of infection control. "Comparing with the CDC rates would be bit unfair because American hospitals invest much more in hospitals and to prevent infections too," says Rosenthal.

"The causes for SSIs are no different in India than in other countries," he says. But while Indian hospitals and doctors are ready to invest heavily in measures to treat infections, but not to invest in controlling infections in the hospitals, he adds. WHO's "Clean Care is Safer Care" programme shows that SSIs is the most frequent type of HAIs in low- and middle-income countries (LMICs) and affects up to one-third of patients who have undergone a surgical procedure. The burden of HAIs is significantly (at least 2-3 times) higher in LMICs than in high-income nations.

A study reveals that in-hospital mortality in India is significantly higher among patients infected with multidrug resistant pathogens such as *Staphylococcus aureus* and *E coli*



Sixteen babies per 1,000 live births in India are infected with neonatal sepsis and one-third of them die for want of drugs that work

Therefore, it does not come as a surprise when hospital-based studies show high incidence of SSIs in India. A study published in the *Journal of Patient Safety and Infection Control* in 2018 says that while global estimates of SSIs have varied from 0.5 per cent to 15 per cent, hospitals in India have consistently shown higher rates ranging from 23 per cent to 38 per cent. This higher incidence of SSIs may be influenced by factors such as pre-operative care, operation theatre environment, post-operative care and the type of surgery, the study says.

Studies also show that the incidence of SSIs was highest after cardiovascular and gastrointestinal surgeries and the most common pathogens found in SSIs were *Staphylococcus aureus, Pseudomonas aeruginosa* and *E coli.*

"The prevention of these infections is a complex process, and requires the integration of a range of preventive measures before, during and after surgery. However, the implementation of these measures is not standardised worldwide. No international/national guidelines are currently established in India for the prevention of SSIs and inconsistency in the interpretation of evidence and recommendations among available national guidelines is frequently identified," says a study published in *Journal of Patient Safety and Infection Control* in 2018.

While antibiotic sensitivity tests are not a requirement, data from in each of these reports indicates that many of these infections were due to multi-drug resistant pathogens, including methicillin resistant *Staphylococcus aureus* and extended spectrum -lactamase producing and carbapenem resistant *Enterobacteria, Pseudomonas* and *Acinetobacter.*

Mohapatra says that patients who contract these infections are more likely to have an extended hospital stay with additional economic costs. This also came out in this INICC study. Extra length

In India, 16 per 1,000 live births are infected with confirmed neonatal *sepsis* and one-third of them die for want of drugs that work. These babies acquired these infections from mothers who got the disease from hospitals

of stay in case of neonatal ICU was 14.7 days for blood stream infections and 38.7 days of ventilator related infections. This means multiple things. One, it increases the expenditure of healthcare. Two, it adds to the misery of patients, and third, it leads to unnecessary utilisation of healthcare services in a country where there are people already lined up and waiting to avail them. According to a 2011 WHO report on patient safety, a multicenter study conducted in ICUs in India there was 11, 8 and 5 days of extra stay by patients due to Ventilator Associated Pneumonia Infections (VAPI), central-line associated Blood Stream Infections and catheter related infections respectively.

These infections, according to WHO, not only increased the number of days of stay, but also contributed to mortality. VAPI became the cause of mortality in 19 per cent cases, while the other two BSIs contributed to 11.6 per cent and 4 per cent respectively.

"A single day stay in an ICU can increase the cost to patients. For countries like India—where out-of-pocket expenditure is one of the highest in the world—it can definitely increase it further," says Mohapatra. According to the 2011 WHO report, the cost associated with hospital-acquired BSI blood stream infections in cardiac surgical patients in a hospital in India is around US $22,873 and represented an excess cost of US $14,818 per case compared with non-infected patients. "Despite a lower device use ratio in Indian ICUs, device-associated HAI rates are higher than what CDC has noted in the US," says the INICC report. This clearly point out that there is something terribly wrong in the way devices are used in Indian ICUs.

The implementation of infection control programmes can prove effective to reduce and control of HAI surveillance, as shown in different studies conducted in the US. Such programmes can result in not only a reduction of 30 per cent in DA-HAIs rates, but bring down healthcare costs as well.

These high HAI rates may reflect the typical ICU situation in hospitals in India and several reasons can explain this fact. "In India, adherence to practice bundles (protocols) is irregular, hospital accreditation is not mandatory, and some of the technology applied is different from that of high-income countries. This situation is further emphasised by the fact that administrative and financial support in public hospitals is insufficient to fund comprehensive infection control programmes. This invariably results in extremely low nurse-to-patient staffing ratios—which have proved to be highly connected to high HAI rates in ICUs and hospital overcrowding, says the INICC study. Besides the devices, surgical equipment require sterilisation. "Many hospitals in India don't have an autoclave for sterilisation and they instead just boil the instruments. This especially happens in peripheral healthcare facilities. Boiling does not ensure that all pathogens attached to the instruments are removed," says Subhojit Dey, a member of the patient safety guideline framework formation committee.

637

hospitals across India have got accreditation from the government. The majority don't

Multiple causes

HAIs were discussed rarely in Parliament. In 2010, former Rajya Sabha member, P Rajeev, asked if the government had evolved patient safety and infection control standards for

government and private hospitals in the country. The then Rajya Sabha member and former Union Health and Family Welfare Minister Ghulam Nabi Azad replied that as far as the three Union Government hospitals in Delhi were concerned—Dr Ram Manohar Lohia Hospital, Safdarjung Hospital and Lady Harding Medical College & associated hospitals—stringent patient safety and infection control standards were being followed. It listed the formation of infection control committees, formulation of infection control guidelines and hand-hygiene guidelines. But Azad's response was only limited to these three hospitals. Similar information about the condition in other hospitals in India is not available. While tough patient safety guidelines to control HAIs were formulated in 2018 during the tenure of former health minister J P Nadda, they are not legally enforceable and remain voluntary.

According to the 2019 *Economic Survey*, only 20 per cent primary health centres (PHCs) comply with Indian Public Health Standards (IPHS) which were introduced under the National Rural Health Mission in 2007. Among the set of norms prescribed, one is to ensure cleanliness in all areas of the health facility as non-adherence can lead to infections. Haryana and Uttar Pradesh were the worst performers, with less than five per cent PHCs following the norms. In contrast, 90 per cent PHCs in Tamil Nadu and 100 per cent PHCs in Andhra Pradesh were adhering to the norms.

Another factor adding to the problem is that any hospital can function without their quality accreditation. Till date, only 637 hospitals have got the National Accreditation Board for Hospitals (NABH) certification across India. "This accreditation provides certain guidelines—including



Hospital Acquired Infection rates reflect the poor hygiene in Intensive Care Units in Indian hospitals

those to reduce HAIs—that a hospital has to follow," says Dey.

Patient rights are also neglected. "When the patient comes to us with a set of infections, s/he is responsible for them. After that, during the course of the stay in the hospital whatever infection s/he contracts, it is the responsibility of the hospital. There are CDC guidelines which clearly state whether an infection was acquired in hospital or it was his/her own. But it is difficult to establish every such parameter in a developing country like India," says Mohapatra.

In many developed countries, if HAIs are found to be the cause of the death and the patient had a medical insurance, then the hospital has to bear the cost of the treatment. This ensures the responsibility of the hospitals. This is not the case in India. An official from CDC's India office opined that frameworks are no use if they are not converted into laws and rigorously enforced.

A faculty member in AIIMS-Delhi microbiology department says, "It is just not general hygiene in hospitals that poses a challenge in India, even personal hygiene of hospital staff is important. However, the medical staff cannot be entirely blamed. While building the hospital, if the contractor forgot that a basin was to be built in the doctor's chamber, you can't fault the doctor. Hand hygiene ensures HAIs go down by 80 per cent of caretaker or any medical staff. We are going to come out a paper on it very soon. It is the most cost-effective and simplest method to reduce HAIs, she says.

But the problem is also in the attitude of medical staff. Whenever you touch a patient, before



Antibiotic susceptibility tests should be conducted before the first antibiotic is administered to the patient

About 50 per cent of antimicrobial use in India has been found to be inappropriate. Strategies to prevent the emergence and spread of healthcare associated antimicrobial resistance is essential

and after, you have to wash your hands. But that sounds tedious to many because they have to take care of a number of patients at a time. In many cases, hand washing is done only after the staff enters and exits the ward, doctors say.

General hygiene of hospitals is also an issue in many hospitals which too can append the infection rate. Flowing drains, defunct water coolers, unclean beds and bedsheets and stinking washrooms are common sight in many hospitals. This is compounded by shortage of personnel. "Key specialists to tackle AMR are in acute shortage. Just like treating an infection is a special job, you need special doctors to treat HAIs. Since HAIs come under the umbrella of AMR, you also need hospital epidemiologists. There are acute shortfalls here too," Rosenthal points out.

Towards patient safety

Long-term implementation of recommended procedures will require concerted efforts to strengthen infection prevention and control capacity among staff in healthcare settings. It is important to find ways to support standardised surveillance of healthcare associated infections in India and link the data to the implementation of infection control policies, interventions and indicators that are suitable for local needs. Demonstrated improvements in infection control practices and reductions in HAIs can help secure the commitment and funding needed to sustain these infection prevention and control programmes.

But the biggest change has to come in the medical fraternity itself and they have to introduce important behavioural changes. "Doctors are realising that antibiotics are failing to provide relief and there is no other treatment available. So they are adapting to the change required to beat HAIs," says Mohapatra. Many facilities have set up hospital infection control committees, although these are working with varying effectiveness. Data from a few facilities in India suggest that implementation of such bundles is feasible and can reduce infection rates.

About 50 per cent of antimicrobial use in India has been found to be inappropriate and strategies to prevent the emergence and spread of healthcare associated antimicrobial resistant organisms are essential. According to ICMR's Antimicrobial Stewardship Program Guidelines, three things are crucial: effective clinical antimicrobial stewardship, meticulous hand hygiene, surveillance and monitoring of antimicrobial resistance, especially in MDR organisms. Other than this, hospital staff should be educated and vaccinated to aid infection control. Patients should be informed about the importance of timely reporting of HAIs. Healthcare professionals can partner with hospital administrators to implement interventions that can minimise medical misadventure, control infection spread and enhance patient care and safety, say the guidelines.

(Names of patients have been changed to protect identity)

MACHINES CANNOT DETECT INACTION

There are a wide array of easy-to-use and affordable devices to detect various bacterial infections. But we need to find the larger solutions to attain a perfect regime

BANJOT KAUR

WHEN HIMANSHU Prasad, 15, caught a cough, his parents dismissed it as usual. But his situation worsened and the boy was taken to a hospital near his home in Bihar's Lakhisarai district. The doctor diagnosed normal chest infection and prescribed levofloxacin, an antibiotic. The drug worked and Himanshu felt better.

But the cough returned in a few weeks. The doctor repeated the drug and the boy was once again back on his feet. When the cough came back a third time, the worried parents took him to Patna. The doctor there suspected tuberculosis (TB) and asked for a sputum smear microscopy test. Himanshu not only tested positive for TB, but had also developed multi-drug resistant tuberculosis, or MDR-TB.

Like Himanshu, 21-year-old Anubhav Shastri of Delhi's VasantVihar lost crucial time in diagnosis. Six months ago, a doctor at a private clinic gave him antibiotics for recurring fever. When high fever did not subside, he was rushed to a posh hospital in Saket. Here, Anubhav's health improved, but only briefly.

Seven days later, he was told to go to a TB hospital. At the National Tuberculosis and Respiratory Research Institute in Mehrauli, his sputum was tested. The result, which came in two days, was negative for TB. The doctor asked for a skin test. That confirmed TB but it took two more days. Anubhav has a TB-infected lump in his chest bone. "Early detection would have saved us a lot of time and money," says his mother.

Technologies on the anvil

Medical diagnostics take time, are costly and often give inconclusive results. So many doctors prefer to administer drugs on poor patients on the basis of symptoms rather than recommending expensive tests. The down-side is that by the time the disease is diagnosed, patients turn resistant to the drugs that should be treating them, or their disease worsens.

The problem has pushed government bodies, private institutes and startups to undertake massive research and innovate in medical diagnostics. The focus is on making affordable devices that give fast and final results, and can be used at the point of care (patient's bedside).

After years of research, the Indian Council of Medical Research (ICMR) is ready with TrueNat, which can remarkably change TB treatment. The innovation can have a big impact on a country often called the global TB capital. According to India TB Report 2019, estimated TB incidence is 2.7 million. Out of these, 58,347 cases are drug resistant. "It is an indigenous, cost-effective and sensitive device

that can detect TB and MDR-TB," says Manjula Singh, a scientist with ICMR. TrueNat gives results within an hour while the conventional tests take at least 24 to 48 hours.

TB is diagnosed by detecting the bacteria in sputum sample. For this, over 14,000 designated microscopy centres across the country use the elementary bright-field microscope. The World Health Organization (WHO) recommends the advanced fluorescence microscope. These are present in big cities but high infrastructure cost restricts its use. The machine most in use is GeneXpert, which gives better, but not hundred per cent result. When the bacterial load is below 10,000 per ml of the sample, standard tests can give erroneous results. "TrueNat is so designed that it will not give false results. It is more reliable than any other test for TB," says Singh.

The device is battery-operated and portable. As it is designed for places that do not get regular electricity, it will work well in primary health centres. GeneXpert is useful, but requires uninterrupted power and air-conditioning. TrueNat will roll out as part of the Revised National Tuberculosis Programme, a government initiative to make India TB-free. "Its cost is not yet finalised," says Singh.

Valetude Primus Healthcare, a startup led by IIT-Delhi associate professor Ravikrishnan Elangovan, is developing two low-cost and low-maintenance diagnostic tools. The devise, SeeTB will reduce sample analysis time by one-tenth. It will be strapped to the microscopes used in the 14,000 designated microscopy centres. "Once it reaches all the centres, we will amplify its reach," he says.

The startup has also designed a device that can detect typhoid and gastroenteritis. A blood culture for testing typhoid takes 48 to 72 hours. The new machine, called iMC2, or immune-Magnetic cell Capture, will give the result in six hours. It is easy to use, portable, highly automated and does not need sophisticated laboratories or trained microbiologists.

"It can be used in resource-poor primary health centres that lack infrastructure and trained personnel," says Elangovan. The two technologies will be in the market soon. "Its cost will be highly competitive and a fraction of the existing tests," he says. These will save time and cost, which are critical for diagnostics.

Vipin Vashishtha, a doctor in Bijnor, Uttar Pradesh, is unable to understand what ails the two-month-old son of Ram Mohan, who lives in Nizamabad, Bijnor. Almost since birth, the infant has been running high fever. He is also losing weight. Mohan has already spent ₹30,000 on visits to doctors and has now admitted the child to a private hospital.

"Tests have not given any conclusive result. We do not know which bacteria or fungi has infected the infant," says Vashishtha. Injected with multiple antibiotics, the little one has developed resistance to all major drugs. As his platelet count dips, Vashishtha's guess is that he may have an infection in the brain.

The doctor now desperately waits for the urine culture result that may identify the bacteria. But he has to wait for three more days. Till then, the child may be given yet another dose of antibiotics. Module Innovations, a Pune-based startup, may have the answer to Vashishtha's problem. It has developed U-Sense, a hand-held, credit card-sized device that can give urine test result in 30 minutes. The device has cavities on its four sides.

When the sample is placed at the centre of the device, the urine flows to the cavities. A simple change of colour confirms which uropathogen— *E coli, Staphylococcus aureus, Klebsiella* or *Enterococcus*—has caused urinary tract infection (UTI).

"This will be a boon for people in villages where the number of UTI cases is high. Since it is a point-of-care test, people do not have to

Between 2014 and 2017, the government spent only 2.28 per cent on research and development in diagnostics



travel for it," says Sachin Dubey, co-founder of Module Innovations.

It would be affordable too, but will reach the market in about five years, after the startup and the government complete clinical validations in different geographical settings. "At present, we are doing field validation in Pune and Rajasthan hospitals. We will also go to public health centres in Rajasthan," Dubey says. Module Innovations is one of the three Indian teams to receive ₹90 lakh each for further research on their innovations. The teams will compete for the UK-based Longitude Prize for diagnostic research and innovation in antimicrobial resistance.

Biotechnology Industry Research Assistance Council (BIRAC), a non-profit set up by the Ministry of Science and Technology too has given £200,000 towards its fund.

NanoDx, another recipient of the monetary grant, has developed Septiflo, which determines if a blood sample is bacteria-infected. The device, which looks like the one used for pregnancy tests, gives results in 10 minutes through a change of colour. Its viability test is going on at Maulana Azad Medical College, Delhi.

"The tool will make a big difference in the treatment of ICU patients. The doctor can quickly know which strain of bacteria is causing the infection and can prescribe specific drugs. It will also cater to neonatal infections. This is important because sepsis is considered the second leading cause of death in neonates," says V Sritharan, head of the department of laboratory medicine at Gleneagles Global Hospitals, Hyderabad. The device, expected to be in the market by the end of 2019, would cost between ₹250 and ₹300.

Bengaluru's OmiX Labs and SpotSense

have together developed a device to diagnose neonatal sepsis, assess its severity and guide antimicrobial treatment. It is the third team to win the monetary grant. The thermometer-like device tests for the level of biomarkers for sepsis in neonatal saliva and then uses an algorithm to calculate the score. The result can be obtained in 60 minutes. It may be launched early next year.

For fever-related illnesses

Malaria which too requires antibiotic treatment is a menace in India. In 2018, malaria claimed 85 lives while over 399,000 cases were reported, shows National Vector Borne Disease Control Programme data. For timely detection of acute febrile (fever-related) illnesses, Faridabad-based Translational Health Science and Technology Institute is developing hand-held devices to test malaria and scrub typhus. A drop of blood when placed on the slide attached to the device will give results in 15 minutes. Identifying the cause of the illness reduces the misuse of antibiotics to treat all kind of fevers.

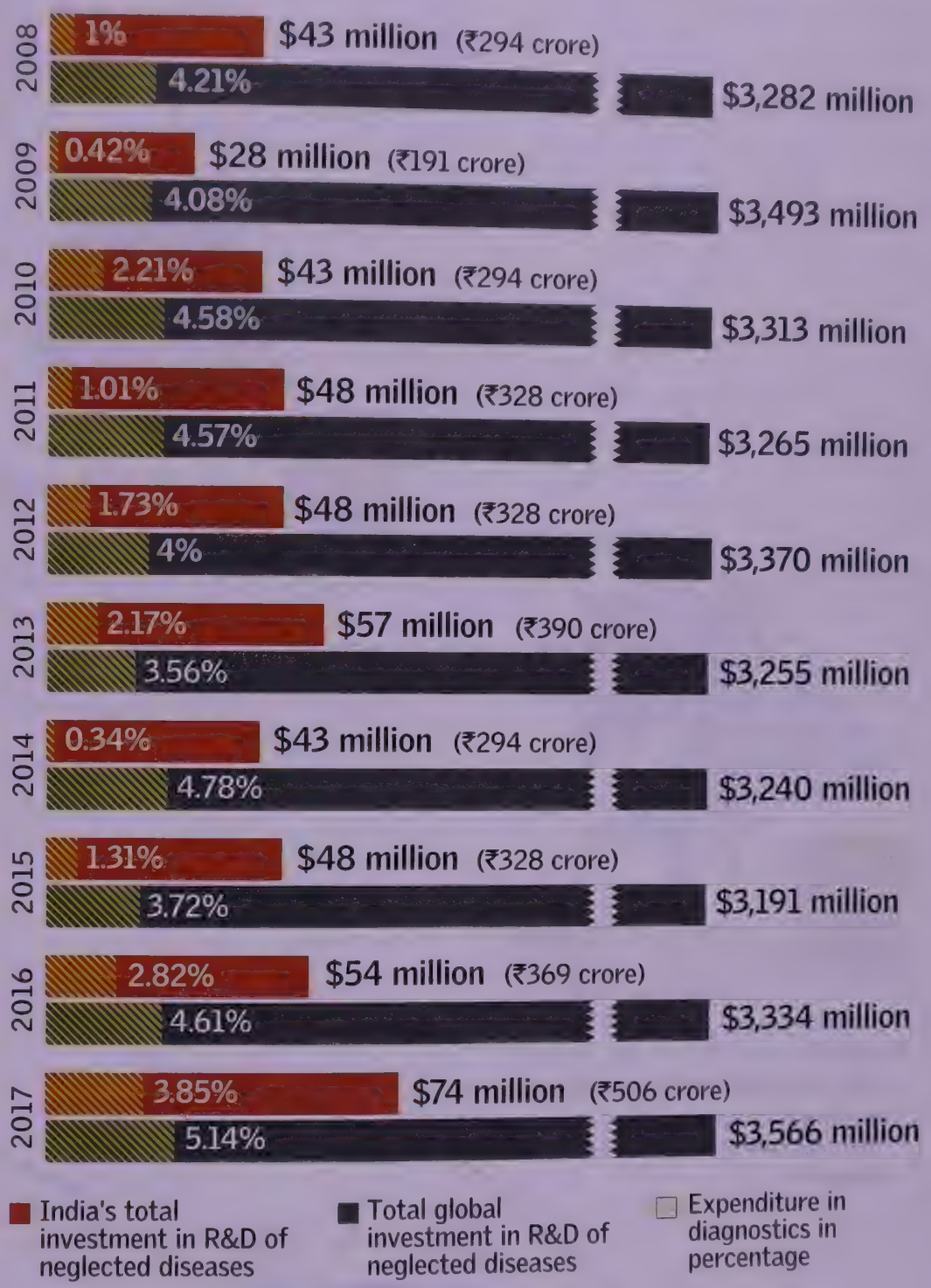
"It is not that point-of-care tests do not exist, but the new devices will give 70 to 100 times better and cost-effective results," says Gaurav Batra, the professor leading the team of researchers. He hopes the kits will become available in two to five years.

To assess if the existing diagnostics are accessible in rural areas, Brookings India Health Monitor conducted a study in 40 primary health centres in three districts—Fatehpur (Uttar Pradesh), Wardha (Maharashtra) and Tumkur (Karnataka). The 2016 study found that tests listed in "essential diagnostic category" were not available in any district. These included tests for TB, malaria, hepatitis B, syphilis and HIV. The study was published in *The Lancet* in 2018.

Rural India spends five times less on diagnostics than urban India. Patients in India spend ₹21,058 crore on medical diagnostics each year, shows the health ministry's National Health Accounts—estimates for India, 2017. This does not include in-patient care.

Detecting funds gap

The country invests a minuscule percentage of R&D funds for neglected diseases on diagnostics. The world average is slightly better



Source: Global G-Finder report, data sourced from WHO

It is unfortunate that only a minute fraction of government's research and development fund goes in medical diagnostics. Between 2014 and 2017, the country spent a total $219 million on research in medicines, vaccines and diagnostics of neglected tropical diseases. Of this, only 2.28 per cent was spent on diagnostics, state reports of G-Finder, a comprehensive data source. The global average is 4.58 per cent.

Hospitals that heal

VIBHA VARSHNEY lists the steps that hospitals should take to maintain healthy facilities



3

KEEP COMMON SURFACES CLEAN
Many bacteria survive on surfaces of counters and tables for months and can spread around when healthcare providers or patients touch these surfaces. Such surfaces should be kept clean and disinfected. New technologies and materials should be explored.



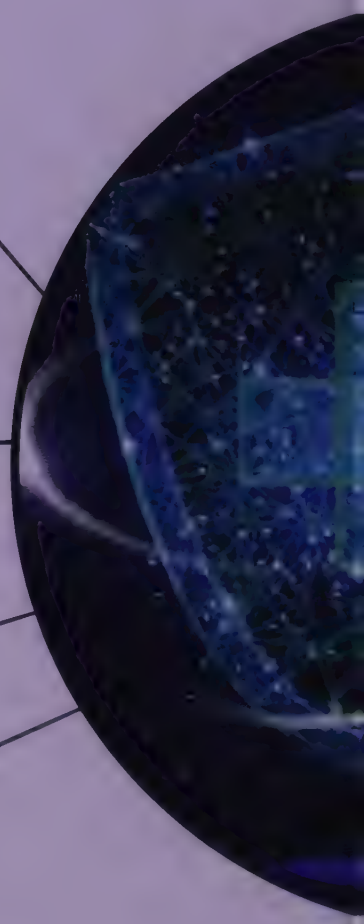
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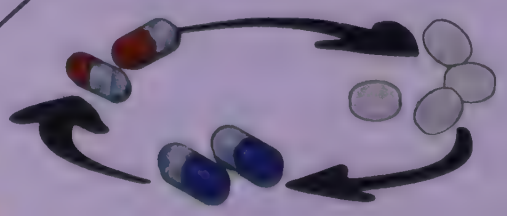
ENSURE HAND HYGIENE
Diseases can be transmitted from one patient to another through health providers. To avoid this, hospitals should set up basic facilities such as basins to wash hands at multiple places. Surgical team personnel should wash their forearms before a procedure and put on sterile gloves.



1

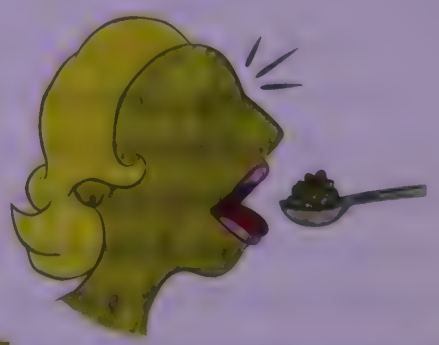
SETTING UP SYSTEMS
Health facilities should establish protocol to ensure infection control. Kayakalp Swachhta guidelines that promote clean hospitals should be enforced by disseminating good practices and replicating role models across countries.





10

USING ANTIBIOTICS RATIONALLY
Cycling of antibiotics where an antibiotic is used as a first-line therapy for all patients for a defined period but is then replaced with a drug of a different class but a similar spectrum of activity for the same duration. This is said to reduce development of resistance.



9

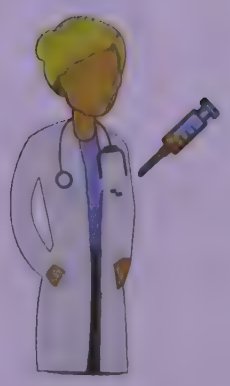
ANTIBIOTIC STEWARDSHIP
Health facilities should be part of antibiotic stewardship programmes to reduce the misuse and overuse of antibiotics by doctors. Hospital authorities should actively create awareness in patients on how they should use antibiotics too.



4

CONTROLLING SPREAD OF DISEASES

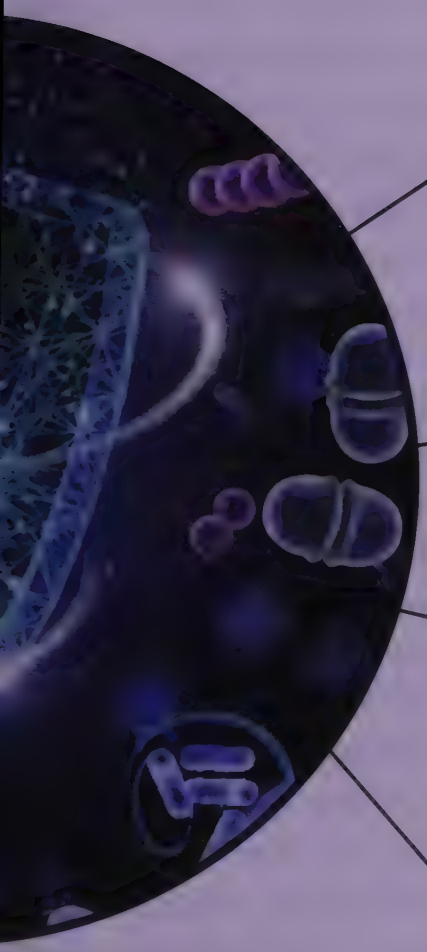
It is imperative that the hospitals take steps to isolate patients with contagious diseases to ensure that they do not cross-infect fellow patients.



5

PROPHYLACTIC MEASURES

The staff at hospitals should be adequately vaccinated wherever possible so that they do not catch the disease and then transmit to patients and co-workers.





6

WASTE MANAGEMENT

Biomedical waste should be treated and disposed according to guidelines. This would ensure infection does not spread.



8

REDUCE HOSPITAL ACQUIRED INFECTIONS

Follow correct treatment protocols as much as possible. For example, removing catheters when not needed ensures that infections are not transmitted.



7

ACTIVE SURVEILLANCE

Hospitals should regularly carry out surveillance in the facility to identify infection sources. Information on outbreaks should be shared with other hospitals and authorities.

DEARTH OF DATA

It is not possible to develop prevention and control protocols for hospital associated infections without a comprehensive database

SANJAY BHATTACHARYA

HEALTHCARE ASSOCIATED Infections (HAIs) are acquired by patients during their stay in a hospital or other healthcare facilities such as nursing homes, outpatient clinics or health centres. Such infections are an important cause of morbidity, mortality, prolongation of hospital stay and increased healthcare expenditure. These also result in increased rate of intensive care unit (ICU) admissions, increased re-hospitalisation rates, and sometimes catastrophic healthcare expenditure. HAIs can affect any age group, including new born babies.

HAIs are not a single disease entity and include a wide variety of infections. Some of the common ones include Catheter Associated Urinary Tract Infection (CAUTI), Ventilator Associated Pneumonia (VAP) and Central Line Associated Blood Stream Infection (CLABSI). These three infection types are also classified within Device Associated Infections. However, there are many other types of HAIs such as Surgical Site Infection, Hospital Acquired Pneumonia and Transfusion Transmitted Infection. Many infections which are generally acquired in the community or outside healthcare facilities may also be acquired by patients within hospitals because of transmission of infectious agents from other patients, staff or visitors. Such infections can include tuberculosis, chickenpox, influenza, food borne and waterborne infections such as typhoid.

Unclean hospitals

The problem of HAIs is not unique to India or other low or middle income countries and affects all countries globally including the developed, the powerful and industrialised economies. It is now a global menace, especially in an era when there is overcrowding in hospitals, extensive use of medical devices, widespread use of broad spectrum antibiotics, and inadequate sanitation or hygiene in healthcare facilities. Many HAIs are caused by superbugs or multi drug resistant organisms. This makes the treatment more difficult and more expensive.

We have heard about superbugs with New Delhi metallo-beta-lactamase 1 (NDM-1) gene. But NDM-1 is not the only antibiotic resistance gene and there are many others. There are Gram positive bacteria such as Methicillin-resistant *Staphylococcus aureus* and Gram negative group of bacteria such as *E coli, Klebsiella, Pseudomonas* and *Acinetobacter* with resistance genes such as OXA48, IMP, VIM, KPC and OXA23. Bacteria are classified as Gram positive or negative on the basis of staining. Many of these superbugs may coexist in the same patient, thus making treatment and infection prevention very difficult.

But not much is known about the prevalence of hospital infection in India. The most significant surveillance project of such infections is currently being undertaken by the All India Institute of Medical Sciences (AIIMS), New Delhi, US-based

Centers for Disease Control and Prevention (CDC) and the Indian Council of Medical Research (ICMR). The multicentric study is coordinated by AIIMS, New Delhi. The importance of this study is its large and varied reach in terms of inclusion of public and private sector hospitals, stringent attention to data quality and quality assurance of processes which lead to data generation and many others. However, the final results of this study would be available only after a few years.

Then there is the international Nosocomial Infection Control Consortium, which is collecting HAI data globally as well as in India. Their latest report was published in February 2016 in the journal *Infection Control and Hospital Epidemiology*. This study included data from 0.23 million ICU patients and analysed information for 0.97 million bed-days.

It is important to understand the concept of bed days in this context. If there are 10 intensive care unit beds in a hospital, the total number of available bed days is 300 (30 days in a month multiplied by 10 beds per day) in a month and 3,650 in a year. This study estimated that the device-associated infection rates for adult and pediatric ICUs to be 5.1 central line-associated bloodstream infections/1,000 central line-days, 9.4 cases of ventilator-associated pneumonia/1,000 mechanical ventilator-days, and 2.1 catheter-associated urinary tract infections/1,000 urinary catheter-days.

This same study reported the following HAI rates from the multicentric pooled data of several neonatal ICUs: 36.2 central line-associated bloodstream infections/1,000 central line-days and 1.9 ventilator-associated pneumonia/1,000 mechanical ventilator-days.

The study reported that the extra length of stay in adult and pediatric ICUs was 9.5 days for central line-associated bloodstream infections, 9.1 days for ventilator-associated pneumonia and 10 days for catheter-associated urinary tract infections. The extra length of stay in Neonatal Intensive Care unit was about 15 days for central line-associated bloodstream infections and 39 days for ventilator-associated pneumonia. This study also reported that HAIs may lead to deaths. The extra mortality (from all causes and not just due to HAIs) was about 16 per cent for central line-associated bloodstream infections, 23 per cent for ventilator-associated pneumonia, and seven per cent for catheter-associated urinary tract infections in adult and pediatric ICUs. The figures were about one per cent for central line-associated bloodstream infections and eight per cent for ventilator-associated pneumonia in neonatal ICUs.

Overcrowding in hospitals, extensive use of medical devices and widespread use of antibiotics is leading to increased cases of hospital infections

Having reliable, accurate, complete, continuous and relevant data about HAIs is extremely important for effective planning which translates into better diagnostic, treatment, prevention and control strategies. Without data, it is not possible to effectively plan for the need of laboratory or radiology-based diagnosis; it is not possible to plan for appropriate treatment protocols or keep adequate stock of necessary medicines or develop focused infection prevention and control interventions.

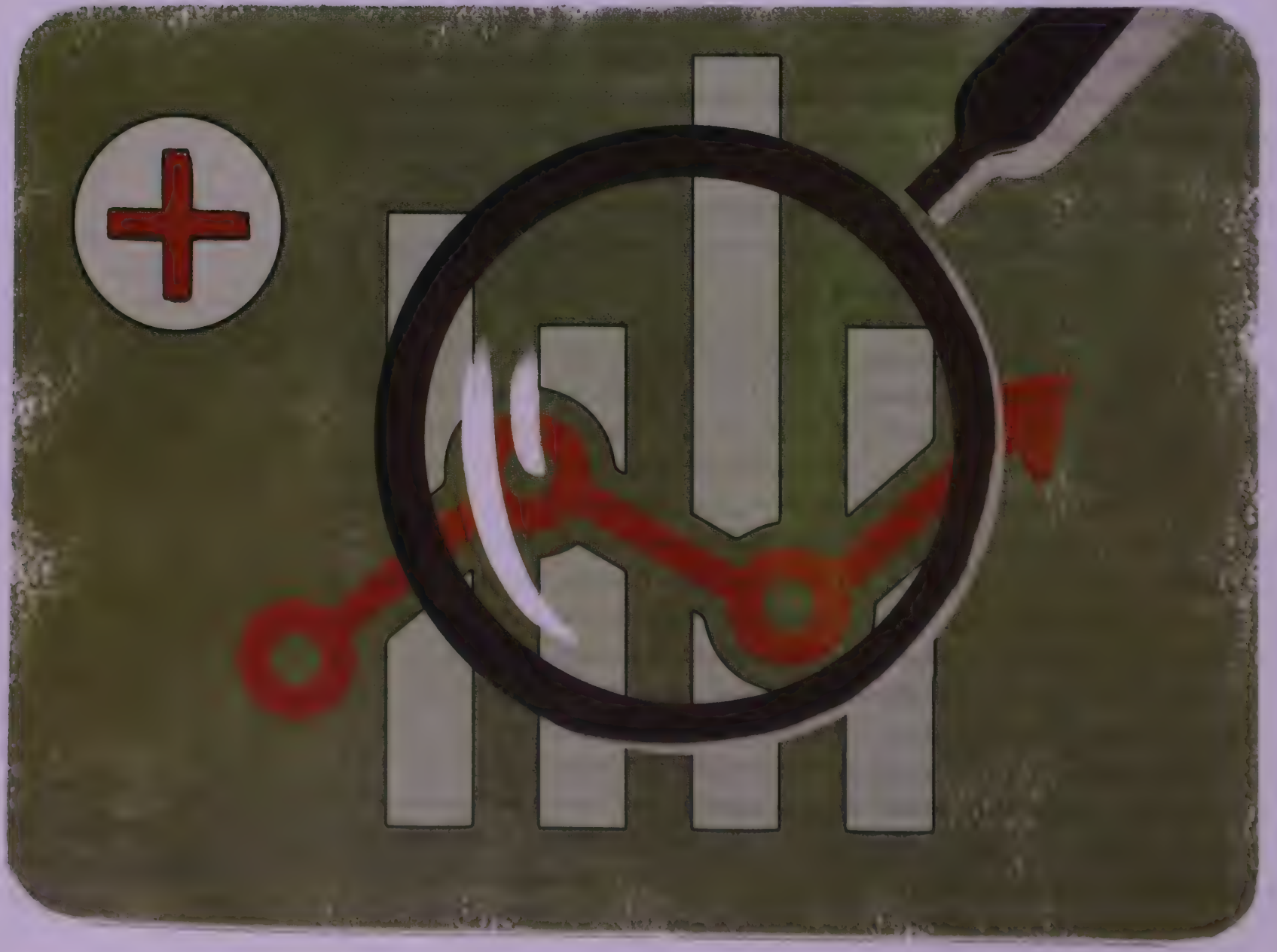
Since in a given hospital there may be many types of HAIs occurring simultaneously or during the same time period affecting various patient categories, it is extremely important that we understand the epidemiology of HAIs in a specific healthcare facility. Epidemiological studies would tell us which type of infections are common, what are the specific agent-host- environmental factors that lead to HAIs, and what the outcome of existing management strategies are. Since resources are always limited

even in the best of centres, knowledge of epidemiology help to prioritise so that we can focus our time, money and energy on certain HAI problems which are most damaging to the patient's well-being.

Data quest

In the case of antibiotic resistance, availability of data is important. Without reliable and accurate data, it is not possible to have short-term or long-term planning with regard to human resource requirement and use medical technologies required to effectively diagnose, treat or prevent HAIs. Data also helps us know incidence and prevalence of HAIs. Incidence implies the number of new cases over a period of time (day, week or month), whereas prevalence denotes total number of new and old cases over similar time periods. If we have access to such data, we can also calculate the risks to patients for a given procedure such as chemotherapy, surgery and endoscopy. This enables doctors and specialists to counsel patients so that more informed decisions can be taken.

In India, reporting of HAIs is still voluntary and not mandatory for hospitals and other healthcare facilities in public or private sectors. Moreover, these infections are still not under the category of notifiable diseases. As a result, there are very few mechanisms in place to track and monitor HAIs in India. In the last one or two decades, some steps have been taken to increase awareness and get some data from the tertiary care hospitals. However, there are currently



very few systems in place to monitor HAIs at the primary or secondary care levels.

There has been some major development with regard to HAI data collection within India in the last five years. These efforts have been led by ICMR and the National Centre for Disease Control (NCDC), New Delhi. Some of these efforts are supported by CDC. Besides going for accreditation to the National Accreditation Board for Hospitals and Healthcare Providers (NABH), hospitals are also required to submit HAI data to the monitors on a regular basis.

However, these efforts have mostly covered tertiary care hospitals in major cities. There is also a greater participation of private sector corporate hospitals within these monitoring systems. In the future, we would have to include all public and private sector hospitals, district general hospitals and nursing homes within these HAI surveillance systems. There should also be adequate legislative support and regulatory supervision to ensure that HAIs reporting becomes mandatory for all hospitals and HAIs are included within the list of notifiable diseases.

At present, HAI data is reported voluntarily mostly as an academic exercise on an ad hoc basis in scientific journals within India. These ad hoc reports may lack scientific rigour, quality control scrutiny and may not report inconvenient truths for political, financial or social reasons. It is very important that we get over this situation and put in place effective systems which collects data according to the best practice recommendations and takes appropriate actions at various levels as and when necessary for better patient safety. We can hope that within the next five years, structured, quality-assured and relevant HAI data would come into the public domain within India and be an important subject of our national agenda for better healthcare for all.

HAI data is reported voluntarily mostly as an academic exercise on an ad hoc basis in scientific journals within India. These ad hoc reports lack scientific rigour

The concepts of Infection Prevention and Control (IPC) have been well known in developed countries for decades. In the case of India, though the theory behind IPC was known and understood decades ago, we lacked in practice and implementing IPC as a routine part of medical education, nursing education and healthcare culture. This has been a major problem and currently efforts are on to overcome this.

Unlike an individual medical or surgical procedure, IPC is something which cannot be done in isolation or as a solo effort. It is always a teamwork and support from the top level healthcare administrators is essential for resource provision or to ensure compliance. The basic technology of IPC such as the Standard Precautions are neither difficult nor expensive. The real hurdle is in their implementation which requires long-term planning and vision with regard to education, sustained and regular training and administrative measures to ensure compliance. In a way IPC is another type of Swachh Bharat Abhiyan.

THE SEARCH FOR ALTERNATIVES

Big pharma has withdrawn from research to find new antibiotics at a time when antimicrobial resistance is increasing. Research on alternatives is at various stages of development

VIBHA VARSHNEY AND MEDHA BHAT

EVERY TWO to three months, Ritam Das, Saroj Chaudhary and Ritu Arora—who are undergraduates and PhD students at the Acharya Narendra Dev College in South Delhi's Govindpuri—travel to some of the dirtiest corners of the city to collect soil samples. They take samples from drains, sewage and even places where people spit. "The dirtiest sample is the best sample," says Ritam Das. But what are they "best" for?

It is this. The group isolates bacteriophages—viruses that can kill the bacteria—from these samples. With these bacteriophages, Das, Chaudhary and Arora along with their professor Urmi Bajpai are trying to find a cure for tuberculosis (TB). Over half a million new cases of rifampicin-resistant TB were reported globally in 2018. Of these, 78 per cent were multidrug resistant TB patients. In 2018, India had 27 per cent of the total global burden, according the *Global Tuberculosis Report 2019*.

Sample soils

Bacteriophages are found naturally where bacteria are present. The group has found effective phages in samples from Dwarka, Faridabad and Janakapuri. Bajpai feels that phages can partly solve the problem of antibiotic resistance. But her work is constrained as she does not have BS4 lab, which costs about ₹65 crore. Without this, the students cannot work directly on the TB bacteria (*Mycobacterium tuberculosis*) and have to work on *Mycobacterium smegmatis*. "We can only get the viral genetic material sequenced and then use computer models to figure out whether they work," says Bajpai. The team is looking for enzymes that work on bacteria. The good news is that the Union government's Department and Science and Technology (DBT) has now started funding research on bacteriophages.

Bacteriophages are not approved for treatment in India though clinical trials are underway. In the Banaras Hindu University (BHU), Varanasi, they are being used to treat non healing wounds. Gopal Nath, who is head of the department of Microbiology at the Institute of Medical Sciences at BHU, says bacteriophages could be used to treat chronic wounds that don't respond to standard treatment. "The creation of a biofilm by the bacterium is a problem as this does not allow the antibiotic to penetrate the wound," he says. A total of 20 patients with chronic non-healing wound between the ages of 12 and 60 were included in the study. *E coli*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa* were isolated from their wounds and a cocktail of customised bacteriophages was topically



applied on alternate days. The team saw that there was significant improvement after three to five doses. Seven of the 20 patients achieved complete healing within 21 days. This significant study was published in *International Journal of Lower Extremity Wounds* in June 2019. Research on bacteriophages was abandoned after the discovery of antibiotics. But now, as resistance against antibiotics is on the rise, there is renewed interest them.

PhagePro, a US-based biotechnology company, is also using bacteriophages against strains of cholera. Their product ProphaLytic-VC can be taken orally and is especially useful for people exposed to cholera infections while they were taking care of sick community members. Intralytix Inc, a Baltimore-based company, is trying to use bacteriophage-based drugs in the field of reproductive medicine and women's health and to develop bacteriophage-based products to modulate vaginal microbiome. One of their products, EcoActiv, targets adhesive invasive *E coli* (AIEC) in patients suffering from Crohn's disease. The clinical trials have entered the second phase at the Mount Sinai Hospital in New York.

Though phage therapy is more specific and customisable treatment, it is also associated with complications. Sankar Adhya, who is with the US-based National Cancer Institute, says, "The phage therapy would not be a drug that your doctor writes a prescription for. It has to be operated by some centres approved by the FDA for chronic infections using custom phage cocktails for specific infections. The centres must maintain large libraries of appropriate phages well characterised, free of toxins and lysogenic capacity. In phage therapy, it has

to include a few days of waiting before the customised medicine is made available for a patient." Researchers are trying to resolve these issues by using enzymes derived from bacteriophages which are responsible for lysing the cell wall to treat the disease. These enzymes are called endolysins and there is little possibility of the bacterium developing resistance against these enzymes. Dinesh Bhandari of the biomolecular interaction centre and school of biological sciences, University of Canterbury, New Zealand, says that endolysin is a better option as unlike bacteriophage, which has to be used in its natural form, endolysin can be engineered to add specific ligands to increase its effectiveness. The engineering of endolysins has opened the roads to utilise these proteins as effective antimicrobials that can provide a solution on the issue of development of resistance. Since the endolysins are enzymes and not the actual organism, there is reduction in the risk of phages becoming endemic. "Phage endolysins are in the final stages of clinical trials. So far, the results are very encouraging. I expect endolysins to be in the market in a few years for general use," says Adhya. One such endolysine is SAL200 which is a candidate drug for the treatment of *Staphylococcus aureus* infection. The efficacy of this was tested in mice treated with a single intranasal administration of the drug or a placebo two hours after infection. It was seen that mice treated with SAL200 exhibited 90-95 per cent survival compared to just 10-40 per cent survival rate in the placebo group. It was also seen that the bacterial loads in the lungs of the SAL200-treated group were significantly lower by 10-fold than those of the control group.

While developing new antibiotics, the search must be to find and develop molecules which are non-toxic to human cells

Abandoning research

Such alternatives are now very relevant as antibiotic resistance is making treatment of even simple diseases difficult. Research on new antibiotics is not yielding much. There are various reasons which have contributed to this snail-paced development of the novel antibiotics sector. The development of an antibiotic takes around 10-12 years with a monetary expenditure of around US $1-3 billion. Unlike medicines for chronic diseases, people use antibiotics only while they are sick and the market for drugs like antibiotic is extremely limited. Adding to the woes is that many of the drugs are failing to get FDA approval. Between 2008 and 2011, just two antibiotics were approved.

The 2017 Antibacterial Clinical Pipeline Report of the World Health Organization (WHO) revealed there are only few innovative antibiotics in development and only nine of the 33 antibiotics developed for priority pathogens belong to five distinct new antibiotic classes. The same year, in February, WHO published a list of 12 antibiotic-resistant bacteria that pose the greatest threat to human health. The list was drawn up in a bid to guide and promote research and development (R&D) of new antibiotics, as part of WHO's efforts to address growing global resistance to antimicrobial medicines. The list highlights, in particular, the threat of gram-negative bacteria that are resistant to multiple antibiotics. The WHO list is divided into three categories, according to the urgency of need for new antibiotics: critical, high and medium priority. The most critical group includes multidrug resistant bacteria that pose a particular threat in hospitals, nursing homes, and among patients whose care requires devices such as ventilators and blood catheters. These bacteria have become resistant to a large number of antibiotics, including carbapenems and

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third generation cephalosporins—the best antibiotics available for treating multidrug resistant bacteria.

Many pharmaceutical companies are withdrawing from R&D of antibiotics and shifting their research to other chronic diseases. And by doing so, they are ditching the joint declaration which was signed by nearly 100 companies, including leading pharmaceutical, generics and biotechnology companies, in Davos, Switzerland in 2016. The agreement focused on setting out a set of common goals and regulations to support the conservation of antibiotics and developing newer and better options for curbing antibiotic resistance. Soon after the signing of this agreement, major pharmaceutical giants like Novartis, AstraZeneca, Sanofi, Allergan and Medicines Co left their R&D on antibacterial.

While leaving the sector, they handed over their incomplete research to small and medium enterprises. For example, Medicines Co sold its portfolio to Melinta Therapeutics Inc, while AstraZeneca spun out its research to a standalone company called Entasis Therapeutics before selling the rest of its antibiotics unit to Pfizer. Sanofi handed over its antibiotic unit to Evotec SE, a German biotech. Novartis AG in 2018 stopped antibiotic research and sold three experimental antibiotics to startup Boston Pharmaceuticals Inc. Allergan Plc too has been trying to divest its infectious disease unit. Of the 42 antibiotics in human trials, only four come from the largest 50 drug companies, according to the Pew Charitable Trusts.

The consequene of this is that number of approved novel antibiotics fell from 19 between 1980 and 1984 to six between 2010 and 2014. However, small companies have come to the rescue and have taken up this research. In India, Hyderabad-based Vitas Pharma aims to develop the next generation antibiotics for multidrug-resistant infections such as hospital-acquired pneumonia, bloodstream infections, complicated skin and soft tissue infections and complicated urinary tract infections.

In Bengaluru, Bugworks, headed by Anand AnandKumar is trying to develop biofilms which can coat the biomedical devices so that the spread of infections via these can be prevented. They hope to reach the proof of concept stage of these biofilms by 2019. The company is working on gram-negative infections as there hasn't been any development of antibiotics against these since 1962, says Santanu Datta, chief scientific officer of Bugworks. Similar initiatives are being undertaken globally too. Spero Therapeuticsin Cambridge, Massachusetts, USA, is working on Gram-negative bacteria as well. The pipeline of the company includes SPR994, an oral carbapenem with in vitro and in vivo activity, SPR720, an oral candidate for antimicrobial treatment of non-tuberculosis mycobacterial lung infections, and SPR206 and SPR741 which are polymyxin analogues to treat MDR hospital infections. Fedora Pharmaceuticals Inc in Canada is trying to discover the antibiotics that target the ESKAPE pathogens (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa*, and *Enterobacter* species). WHO has also identified these as pathogens where attention is most needed. Nacubactam, developed by Fedora Pharmaceuticals, is a Phase 3-ready beta-lactamase inhibitor which works through multiple mechanisms of action, inhibiting a number of beta-lactamase enzymes as well as certain bacterial cell wall enzymes.

Other than researching and formulating conventional antibiotics, researchers are also searching for breakthroughs in diverse and unexpected places. Some of the potential antibiotics include the blood of Komodo

The creation of biofilms by bacteria is the problem as this does not allow the antibiotic to penetrate the wound



dragon, which scientists believe have some potential antibiotics. Or the leaf cutter ants, which utilise bacteria to guard their nests and even the dirt which we have under our feet. The challenge is to find and develop molecules which are non-toxic to human cells. Traditional antibiotics do not accumulate in the environment, preventing any sorts of biomagnification.

Here, the use of compounds derived from plants could provide a reprieve. These already provide an easy alternative to antibiotics when it comes to animal health. These chemicals are added to the feed to remove the microbes infecting the animals; improve the digestibility of food; and, make nutrients available in the feed. These products include herbs and spices like garlic, anise, cinnamon, coriander, oregano, chilli, pepper, rosemary, thyme etc, essential oils or oleoresins and water-soluble polyphenols (flavonoids).

Most of the studies have concluded that plant extracts act well on the Gram-positive bacteria as compared to Gram-negative bacteria. In bacteria that infect humans, ethanolic extracts of plants like *Punica granatum* (pomegranate), *Syzygium aromaticum* (clove), *Zingiber officinales* (ginger) and *Thymus vulgaris* (thyme) have been found to be potentially effective against *Bacillus cereus, Staphylococcus aureus, E coli, Pseudomonas aeruginosa* and *Salmonella typhi.*

There are many other natural products that researchers are working with. For example, researchers are experimenting with bacteriocin, a protein derived from a bacteria, which are lethal to other bacteria. These peptides, produced by the ribosomes of the bacteria,

when released can result in inhibition of growth of closely-related species and have been exploited for their use in the food industry for lone. Their mechanism of action is similar to that of phage lysins—it breaks in the bacterial membrane and leads to lysis. These also have an additional advantage of being highly resilient to extreme environments such as high heat and UV exposure. These have also a lower potential to lead to the development of resistance in the microbes. Another edge of these over the traditional antibiotics is that they do not accumulate in the environment, preventing any sorts of biomagnification. However, they have only been tested on animals so far.

However, the lack of sufficient investment has been a significant problem in the development of bacteriocins. Rolf Joerger of the department of animal and food sciences, University of Delaware, USA, says, "I do not know of a case where a bacteriocin has been applied medically, though the application of nisin—an antibacterial compound in food is common. Even some kinds of toothpaste apparently have bacteriocin-type ingredients." However, the effectiveness of the bacteriocin in animals is of relevance too as the ability to control the spread of pathogen on farm can help to reduce the risks of contact with the human population.

Along with these, the renaissance of techniques like the usage of antibacterial metals, minerals and nanoparticles in the antimicrobial industry is required. These have a broad spectrum of antibacterial activity and low generation of resistance. Metals like copper , zinc, and silver disrupt the functioning of the bacterial cell by generating reactive oxygen species, damaging the DNA and hampering the function of bacterial proteins, whereas Iodine works by reacting with unsaturated fatty acids in the lipid bilayer of the cell wall to cause leaks, as well as inactivating nuclear materials through coagulation.

A research paper *Recent Advances in Antimicrobial Hydrogels Containing Metal Ions and Metals/Metal Oxide Nanoparticles* states that incorporation of metals and metal oxide nanoparticles into hydrogels not only enhances the antimicrobial activity of hydrogels, but also improves their mechanical characteristics. The addition of inorganic nanoparticles can be helpful in providing antibacterial properties to the hydrogel.

However, cases of development of resistance of the *Salmonella enterica* serovar *Typhimurium* towards silver has been observed indicating that the rampant usage of metal ions in almost everything has taken its toll on yet another weapon against antibiotic resistance. Raymond J Turner, a professor at the University of Calgary, Canada, says, "We have lots of silver-resistant clinical isolates now like *E coli, Pseudomonas* and *Klebsiella*. Bacteria can evolve resistance to MBA (metal based antimicrobials) as easily as they do to antibiotics. And resistant genes for most metals have been around since the 1980s."

He adds on to say, "I believe metal-based antimicrobials have the best use in targeted infection control. Unfortunately, we have seen the market mongers go crazy with the use of silver in clothing, fabrics and coatings. People now have athletic clothing coated with silver to prevent them from stinking, but of course, they are developing silver resistance on their bodymicrobiome and when they actually need is an Ag-bandage, it does not work."

A lot has been said about what we have at hand to fight this war against resistant microorganisms, but there are methods can be taken up as a preventive measure to reduce the incidence of such diseases. George Y Wu, director of the hepatology section at Uconn Health, Connecticut, USA, says, "Prevention is always better than cure where possible. Antibiotics should be reserved for treatment, not prevention," he says.

FIGHTING RESISTANCE

Microbes will always win the war against humans. But the immediate battle must be to effectively manage the sale and use of antibiotics, keep the environment clean and continue the search for safer alternatives to contain diseases that cannot be treated with existing antibiotics

VIBHA VARSHNEY



IF YOU want to understand the havoc a small bacterium can wreak, look at *Acinetobacter baumannii*, a tiny, rod shaped, Gram-negative being that now lords hospitals and healthcare facilities around the world. It infects intensive care units (ICUs) where it has colonised equipments like ventilators and even the handrails around the patient's bed. Though hospital-acquired pneumonia is the most common infection caused by *Acinetobacter baumannii*, it is now also implicated in infections of the central nervous system. It equally attacks skin and soft tissue and bones. The bacterium increases the rate of mortality, medical costs and the length of stay patients spend in hospitals. In an ICU of a tertiary care hospital in Karnataka, of the 220 patients studied, 91 had *Acinetobacter* infections. These patients ended up staying eight extra days (20 days *v* 12 days) and spent nearly double the amount of money (₹125,862 *v* ₹68,228) than those patients who did not have the infection, the researchers reported in *Perspectives in Clinical Research* in 2016.

Doctors at the All India Institute of Medical Sciences in Delhi studied the rate of antimicrobial resistance in *Acinetobacter* spp and changes in their resistance pattern over a period of five years (2012–2016) in trauma patients. Of the total 16,210 isolates obtained throughout the period, *Acinetobacter* spp accounted for almost 30 per cent and 98.5 per cent of these were *Acinetobacter baumannii*. The highest level of resistance was observed against ciprofloxacin (96 per cent), followed by cefepime (95 per cent), ceftazidime (95 per cent), piperacillin (95 per cent) and amikacin (92 per cent). *Acinetobacter baumannii* is now carbapenem-resistant and the only antibiotic that somewhat works is colistin. Indeed, we are going back to the pre-antibiotic era.

The call of death

There are figures to show the enormity of the problem. At present, at least 0.7 million people die each year due to drug-resistant diseases, including 0.23 million people who die from multidrug-resistant tuberculosis. By 2050, the annual number of deaths due to antibiotic resistance could be 10 million and experts estimate that one-third of these would be in India. A World Bank assessment published in March 2017 estimated that AMR would exert a drag on global GDP—between 1.1 and 3.8 per cent points between now and 2050. By 2030, antimicrobial resistance could force up to 24 million people into extreme poverty. But the patchiness of data makes it difficult to quantify the AMR crisis any further. What we can say is the problem of antibiotic resistance is set to become bigger due to interplay of multiple factors. For example, there is evidence that climate change will increase the spread of infectious diseases and will also make it difficult to treat the infections.

Bacteria multiply rapidly and easily adapt to the antibiotic residues in the environment. Global warming is increasing the pace of reproduction. Researchers from University Medical Center in Göttingen, Germany, conducted a 30-country observational study on six-year prevalence of carbapenem-resistant *Pseudomonas aeruginosa* (CRPA), *Klebsiella pneumoniae* (CRKP), multidrug resistant *Escherichia coli* (MREC), and Methicillin-resistant *Staphylococcus aureus* (MRSA) and found that these were more prevalent during the warm-season mean temperature. "These results reveal two aspects: climatic factors significantly contribute to the prediction of AMR in different types of healthcare systems and societies, while climate change might increase AMR transmission, in particular carbapenem resistance," the researchers said at the 29th European Congress of Clinical Microbiology and Infectious Diseases in Amsterdam, the Netherlands in April 2019.

50%

of antibiotic use is inappropriate and, therefore, is not needed, says the WHO

Before this, a study from the US had already found this linkage. A team of epidemiologists from Boston Children's Hospital, USA, and the University of Toronto, Canada, found higher local temperatures correlated with a higher degree of antibiotic resistance in common

bacterial strains. They looked at antibiotic prescription rates and found that increased rate of prescriptions were associated with increased antibiotic resistance across all pathogens investigated. They then compared this database to local temperatures and found a strong correlation between higher local average minimum temperatures and antibiotic resistance. Local average minimum temperature increases of 10 degree C were found to be associated with 4.2, 2.2 and 3.6 per cent increase in antibiotic resistant strains of *E coli*, *K pneumoniae*, and *S aureus*, respectively. The findings were published in *Nature Climate Change* in May 2018. Climate change is likely to compound the problem in the developing world where access to medicines is already poor. A 2019 report by US-based Center for Disease Dynamics, Economics & Policy (CDDEP), *Access Barriers to Antibiotics*, highlights how a majority of avoidable deaths due to resistance occur in low- and middle-income countries due to drug shortage. New and more effective drugs are also not available. In Sub-Saharan Africa, poor access to existing drugs is exacerbated by the fact that less than 24 per cent of new antibiotics are registered here due to regulatory hurdles. Of the 21 new antibiotics entering markets between 1999 and 2014, less than five were registered in most countries of sub-Saharan Africa.

What is available is misused in poor countries as they mask the absence of healthcare infrastructure. The World Health Organization (WHO) estimates that 50 per cent of antimicrobial use is inappropriate and, therefore, is not needed. In India, 80 per cent of antibiotics used are outside hospitals. Antibiotic use is increasing steadily in the country. According to the 2015 report by CDDEP, an Indian consumed about 7.4 antibiotic pills (per year) in 2000 and this increased to about 11.7 antibiotic pills in 2010. Adding to the problem of misuse is the presence of falsified or substandard antibiotics. According to a 2017 report by WHO, 7.2 per cent of antibiotics tested were substandard or falsified. This is increasing resistance because of under dose leading to unnecessary use of second-line drugs. These are again a problem in poor and developing countries. While data on substandard antibiotics in India is absent, a recent report on the Union government's affordable medicine scheme, Pradhan Mantri Janaushadhi Pariyojana, found 25 batches of drugs to be of substandard quality since January 2018. These included the antibiotic ciprofloxacin.

Feeble moves

In India, the problem of antibiotic resistance continues unabated despite a decade-long campaign to promote rational use of antibiotics. After the discovery that antibiotic resistance conferring enzyme NDM-1 originated in India, a National Task Force on AMR Containment was set up in 2010 to review the manufacture, use and misuse of antibiotics in the country. The task force was mandated to recommend the design for the creation of a national surveillance system; initiate studies documenting prescriptions patterns; and, establish a system to monitor the use of antibiotics in humans, veterinary and the industry. The group also had to recommend intervention measures towards rational use and strengthen diagnostic methods for antimicrobial resistance monitoring. The result was the formulation of the National Policy on AMR Containment in 2011. The "Jaipur Declaration" was signed in September 2011 by health ministers of countries in the South East Asia Region of the World Health Organization. This recognised the importance of national governments giving this issue utmost importance to preserve efficacy of the antimicrobial agents. Then the

Overuse is not the only problem. Exposure to even minuscule amounts of antibiotics can trigger the evolution process in the microbe



The concept of antibiotic stewardship needs to be popularised among all stakeholders in the health industry

"Chennai Declaration" was signed by a consortium of the Indian Medical Societies in 2012. The aim was to develop a consensus and decide on a road map to reduce antibiotic resistance. The National Programme on Containment of Anti-Microbial Resistance was launched under the 12th Five-Year Plan (2012-2017). India worked quickly when, in 2015, the World Health Assembly directed member countries to align their National Action Plans on AMR with the Global Action Plan on Antimicrobial Resistance (GAP-AMR) by May 2017. India set up the Intersectoral Coordination Committee, Technical Advisory Group and Core Working Group on AMR for technical coordination and oversight in September 2016 and the National Action Plan on Antimicrobial Resistance (NAP-AMR) was released by this group on April 20, 2017. This was done at the inter-ministerial consultation aimed at adopting a holistic and collaborative approach towards prevention and containment of AMR in India and increasing cooperation between various ministries. The Delhi Declaration on Antimicrobial Resistance was also endorsed here by the Union government.

The National Health Policy, approved in March 2017, also addressed antimicrobial resistance as one of the key issues and gave priority to development of guidelines on antibiotic use, limiting the over-the-counter use of antibiotics, restricting the use of antibiotics as growth promoters in livestock, and pharmaco-vigilance, including prescription audit inclusive of antibiotic usage in hospitals and community. To promote appropriate use of antibiotics in humans, the Red Line campaign was launched in India in February 2016 to curb over-the-counter sale of antibiotics. Under this campaign, a red line is printed on antibiotic packages as warning. In another effort to create awareness, Department of Biotechnology and Wellcome Trust initiated the "Superheroes against Superbugs" programme in 2018. This involved schoolchildren in Hyderabad who were provided information related to microbes, infections, antibiotics and resistance using interactive

games and creative activities. The children developed comic-book stories based on different problems related to antibiotic resistance, such as using antibiotics for viral infections or without a doctor's consultation.

To promote safe and appropriate use of antibiotics by doctors and hospitals, the concept of antibiotic stewardship was popularised by ICMR which developed Anti Microbial Stewardship Program (AMSP) guidelines to help hospitals create their own stewardship programme. Under this, doctors have to obtain appropriate cultures before prescribing antibiotics and review the impact after 48-72 hours and continue only if the drug is working. In countries with effective antibiotic stewardship, there has been a decrease in AMR. For example, while in India Methicillin resistance in *S aureus* went up from 29 per cent in 2008 to 47 per cent by 2014, in countries with effective antibiotic stewardship, the proportion of Methicillin-resistant *S aureus* isolates has been decreasing. Similarly, in Australia, use of fluoroquinolones has been controlled through stewardship its use is restricted by guidelines favouring alternative options. As a result, fluoroquinolone use here is one of the lowest in high-income countries: less than 0.6 defined daily doses/1000 inhabitants per day compared to 1 defined daily dose/1000 inhabitants per day in Europe. Rate of resistance to fluoroquinolones is lower than that seen in Europe. In 2010, only 5.2 per cent of *Escherichia coli* isolates from community-acquired infections were fluoroquinolone-resistant in Australia, whereas for most European countries this is well above 15 per cent. In India, stewardship programmes are tougher to implement as these need to include the informal healthcare providers. An estimate suggests that there are more than 1.6 million such practitioners in the country. Another estimate from 100 villages in Madhya Pradesh shows that 64 per cent of healthcare providers were private providers and 70 per cent of them had no medical qualification. These 70 per cent accounted for 77 per cent of healthcare needs.

Technologies, which help doctors make the right decisions regarding the prescription of antibiotics, are also being promoted. The health ministry released the National Treatment Guidelines for Antimicrobial Use in Infectious Diseases which advise doctors to increase the use antibiotics in the "Access" group which are cheap and reduce the use of antibiotics from the "Watch" and "Reserve" groups. These categories are also being kept in mind in the National List of Essential Medicines.

Along with rules and regulations, the government of India has also set up a system for AMR surveillance. This is a network of 30 labs across the country under the National Centre for Disease Control (NCDC). By October 2018, the network had labs in 20 state medical colleges from 18 states. The authority plans to set up five more labs by 2019-20. These labs collect and submit data on seven priority bacterial pathogens—*Klebsiella* spp, *E coli*, *Staphylococcus aureus*, and *Enterococcus* spp, *Pseudomonas* spp, *Acinetobacter* spp, *Salmonella enterica* serotypes *Typhi* and *Paratyphi*—of public health importance to determine the magnitude and trends of AMR in different geographical regions.

The Indian government is also promoting the principles of "One Health" in the country. The One Health India Conference in February, 2019, launched the "One Health" Initiative—an intersectoral approach to tackle the most urgent health threats in the country—brought together stakeholders from the Department of Biotechnology (Ministry of Science and Technology), Department of Agriculture Research and Education and Department of Animal Husbandry, Dairying & Fisheries (Union Ministry of Agriculture & Farmers' Welfare) and Department of Health Research and Department of Health and the Family Welfare (Ministry of Health & Family Welfare). The main objective of the conference was to formulate a roadmap for response, preparedness, and management of current regional, national and global health challenges using a "One Health" collaborative approach.

This is in line with the recommendations of the UN's High-Level Meeting on Antimicrobial Resistance that took place in 2016. The Interagency Coordination Group (IACG) on Antimicrobial Resistance was set to evolve a blueprint to fight antimicrobial resistance. The group came out with its report in April 2019 and recommended a "One Health" response. Under this, while the countries need to ensure that plant and animals that need antimicrobials, vaccines and diagnostics are not deprived, they also have to phase out their use for growth promotion. The group also recommended that funds should be made available to support innovations in new antimicrobials, diagnostics, vaccines and waste management tools.

To an extent, intersectoral approach is already being followed in India. In case of meat production, which accounts for 73 per cent of global antibiotic use, a number of steps have been taken to reduce the use of antibiotics in rearing animals. The Food Safety and Standards Authority of India (FSSAI) notified the Food Safety and Standards (Contaminants, Toxins and Residues) Amendment Regulations, 2018 specifying the "Tolerance Limits" of antibiotics and other veterinary drugs in meat/meat products, poultry, fish and milk. Through this amendment, the existing regulations have been further expanded to include new tolerance limits for 103 antibiotics and veterinary drugs in meat/ meat products (including poultry and fish) and milk. Food business operators had to comply with these provisions by January 1, 2019.

In 2017, the Indian Council of Agricultural Research (ICAR) initiated the Indian Network for Fisheries and Animal Antimicrobial Resistance with 18 labs in collaboration with the Food and Agriculture Organization (FAO). This is an advisory body comprising ICAR officials, senior scientists and external experts, which reviews data generated by the labs. The National Institute of Veterinary Epidemiology and Disease Informatics, Bengaluru coordinates the overall technical and data management operations of the network. The same year, ICMR and ICAR developed a Standard Operating Manual for veterinary antimicrobial susceptibility testing. Recently, the Union Ministry of Health and Family Welfare (MoHFW) prohibited the sale, manufacture and distribution of colistin and its formulations in food producing animals, poultry, fish and animal feed supplements in July 2019. This step was taken to ensure that colistin remained effective against human diseases. Colistin is the last resort antibiotic for humans and a "highest priority critically important antimicrobial".

To reduce industrial pollution, in October 2019, the department of pharmaceuticals asked associations of pharma companies like Indian Drug Manufacturers' Association, Organisation of Pharmaceutical Producers of India, Indian Pharmaceutical Associations and other associations to urge their members to put a check on pollution. The department also revealed that the Central Pollution Control Board (CPCB) has set up an expert committee to draft standards for antibiotic residue in industrial effluents, and the draft is now close to finalisation. India's Department of Biotechnology too is supporting research on reducing AMR in environment from antimicrobial manufacturing waste. For this they have joined hands with the Natural Environment Research Council (NERC) of UK. NERC has committed £3.8m to support eligible UK-based researchers and DBT is matching the amount to support eligible Indian researchers. Managing the waste of this industry is important considering that 80 per cent of antibiotics sold by multinational antimicrobial companies in global market are manufactured in Asia. There are at least 40 antibiotic pharmaceutical ingredient manufacturers and at least 250 pharmaceutical formulation companies manufacturing at least one antibiotic in India. On the research front, WHO has also identified 12 pathogens for which new antibiotics are needed. Researchers in India too are working accordingly.

12

The number of microbes WHO has identified for which new antibiotics are needed immediately

Despite all these initiatives, the level of antibiotic resistance is on the rise in the country. In August 2019, the Indian Council of Medical Research released the findings of Antimicrobial



Antibiotic resistance increases the rate of mortality, medical costs and the length of stay in hospitals

Resistance Surveillance Network for the year 2018. During the year, the total number of isolates studied were 60,497. The results show that there is an increasing resistance in Gram-negative bacteria. There is combined resistance to third-generation cephalosporins and fluoroquinolones and increasing carbapenem resistance which is worrisome point out researchers who are part of the network in a paper published in Indian Journal of Medical Research in June 2019. Gram-negative bacteria showed an increasing resistance to last resort drugs such as carbapenems and colistin. For example, E coli was 75-80 per cent resistant to broad-spectrum antibiotics such as third-generation cephalosporins and fluoroquinolones. Despite clear evidence of how antibiotic resistance is affecting patients, doctors continue to prescribe indiscriminately. A paper published in *PLoS ONE* showed that while prescription rate for antibiotics in India less when compared to European countries, the percentage of prescriptions with cephalosporins and quinolones (38.2 per cent and 16.3 per cent in India were significantly higher than the United States (14.0 per cent and 12.7 per cent). The prescription rates were the highest for children aged 0–4 years and the lowest in the age group 10–19 years. Cephalosporins were the most commonly prescribed antibiotic across all diagnoses except for disorders of the urinary system where quinolones were more commonly prescribed. The third line of antibiotics which should be prescribed only at hospital-level, usually in ICUs, are being prescribed at primary care level, researchers found.

Falsified or substandard antibiotics make up seven per cent of antibiotics in the global market, which can increase resistance in microbes

There are only 10 years left for the world to meet the Sustainable Development Goals. Antibiotic resistance can derail the efforts of countries to meet the targets

What can work

The Indian government has to do much more as the bacterium is a worthy opponent. The biggest problem is that we live in a contaminated environment. Safe water and modern sanitation can reduce bacterial infections by as much as 60 per cent and reduce the need for treatment with antibiotics. But it is very difficult to clean the environment as even low concentrations of the drug can lead to resistance. Wastewater treatment methods using disinfectants such as chlorine dioxide and monochloramine are not very effective. A team at the University of Washington found that these methods barely damaged the blt gene responsible for pumping antibiotics out of *Bacillus subtilis*. This gene makes the bacterium resistant to a variety of common antibiotics. Instead, methods such as UV light, ozone and chlorine can prevent the spread of antibiotic resistance by both deactivating the bacteria and damaging the resistance gene, the researchers recommend in their paper published in *Environmental Science & Technology in February 2019* . The team is developing a model to properly treat any antibiotic resistance gene. Another method for reducing residues in the environment is to use hyperthermophilic composting methods, where compost is heated to a temperature of 90°C. During the process, bacteria are killed. Hyperthermophilic composting, therefore, has the potential to make compost products safer says the research published in Environmental Science and Technology on February 8, 2018.

Unless environmental triggers to antibiotic resistance are controlled, it would be difficult to control resistance. An opportunity lies in the United Nation's Sustainable Development Goals (SDGs). The environmental triggers that are leading to resistance are part of SDGs. In goals on poverty (SDG 1), food production (SDG 2), health (SDG 3), economic growth (SDG 8), inequality (SDG 10) and the environment (with specific reference to SDG 6 on water, SDG 14 on life below water and SDG 15 on life on land), antibiotic resistance has not been given adequate attention. However, course correction is underway. In 2019, WHO has proposed to track two priority pathogens in bloodstream infections namely *Escherichia coli* and *Staphylococcus aureus*. These would serve as sentinels of progress. This indicator connects the Monitoring and Evaluation Framework put together by WHO, FAO and the World Organization for Animal Health. The indicator is part of target 3d which is to strengthen the capacity of the countries for early warning, risk reduction and management of national and global health risks. While using AMR as an indicator to track progress on SDGs is an important stepping stone. But we must keep in mind the fact that only 10 years are available for efforts to take effect on the ground. However, the very fact that there are multiple areas in the SDGs where action on AMR can take place is an opportunity.

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WHAT SHOULD WE DO?

To fight antibiotic resistance efficiently, a One Health approach that incorporates diverse stakeholders from farming, veterinary, medical and environmental sectors is essential

RAMANAN LAXMINARAYAN, ISABEL FROST

ALTHOUGH OFTEN viewed as a medical problem, antibiotic resistance is really one of managing a shared resource to maintain antibiotic effectiveness.

Any conservation effort to protect this global resource would also necessarily need to be global. India—with its combination of large population, rising incomes that facilitate purchase of antibiotics, high burden of infectious diseases, and easy over-the-counter access to antibiotics—is an important locus for the generation of resistance genes. The multi-drug resistance determinant, New Delhi Metallo-beta-lactamase-1 (NDM-1), emerged from this region to spread globally. Africa, Europe, and other parts of Asia have also been affected by multi-drug resistant typhoid originating from South Asia. The containment of antimicrobial resistance (AMR) in India is, therefore, central to the global effort to address this threat.

In India, over 56,000 newborn deaths each year due to sepsis are caused by organisms that are resistant to first line antibiotics. Also, an estimated 170,000 deaths from pneumonia in children under five can be averted with timely access to effective antibiotics. While rising rates of resistant infections are a threat, many deaths are attributable to the lack of access to basic antibiotics. We need to balance excessive and inappropriate use, a key driver of antibiotic resistance, while ensuring live-saving medicines are available to those who need them.

Clean up first

Beyond access to effective antibiotics, reductions in India's mortality from infectious diseases will be brought about by improvements in vaccination coverage, access to clean water, adequate sanitation and improved hygiene. Half of the south Asian population lacked access to basic sanitation in 2018. The Swachh Bharat Mission in India has improved access to toilets in many areas.

However, efforts must be made to bring about behavioural changes so that people use these toilets. One estimate found that improvements to the infrastructure required for and access to clean water, adequate sanitation and quality hygiene in India could result in a reduction of 590 million diarrheal cases by 2020 that would have been treated with antibiotics.

Vaccination has been shown to reduce the transmission of AMR infections and the volume of antibiotics consumed due to both appropriate treatment of bacterial infections and inappropriate treatment of viral infections. India has undertaken many activities like Mission Indradhanush—to address low vaccination coverage—strengthened micro-planning and additional mechanisms to improve monitoring and accountability. Yet improvements in coverage are still needed; coverage of the DTP3 vaccine against diphtheria, tetanus and pertussis is 89 per cent, for the measles vaccine, the first dose, MCV1, has coverage of 90 per cent, and

the second dose, MCV2, of 80 per cent, the Hepatitis B vaccine, HepBB, has coverage of 54 per cent, and for HepB3, it is 89 per cent.

As antibiotics are commonly given to patients presenting with a fever, any vaccine that reduces the incidence of febrile patients will lower antibiotic consumption. In many countries the introduction of the vaccine against *Haemophilis influenza*, eliminated Hib meningitis, bacteremia, pneumonia, and epiglottitis, including drug-resistant infections—Hib3 coverage is 89 per cent in India. Rotavirus is the most common cause of severe diarrheal disease in young children worldwide and a cause of inappropriate antibiotic use, yet coverage of the vaccine, RotaC, is just 35 per cent in India.

When the pneumococcal conjugate vaccine (PCV) was rolled out in South Africa, it was related to an 82 per cent reduction in the rate of penicillin-resistant pneumococcal disease in children. PCV coverage in India is currently six per cent, as many states are yet to adopt it into immunisation schedules. Trials are currently underway for vaccines at different stages of development against typhoid, dengue and malaria which have the potential to reduce antibiotic prescribing and the incidence of drug resistant infections in India.

Flaws in medical fraternity

Consumption of antibiotics is the key driver of resistance. Effective management of this limited resource will ensure antibiotics are only used when appropriate and necessary. Many medical practitioners lack formal training in India and 70 per cent of primary healthcare is delivered by such individuals. Sales companies target both doctors as well as those acting in a medical capacity without required qualifications. They may be given gifts, such as medical equipment, televisions, travel or cash not to switch to competitors or to incentivise the sale of antibiotics to dispensers. Pharmaceutical sales representatives are a key source of updates and information for prescribers, but the information they provide may be biased and motivated by commercial considerations to promote antibiotic sales. Efforts in India to address the high levels of unqualified health workers by offering training courses will need to be monitored closely for success.

Even trained doctors worry that patients may not return if they are not prescribed antibiotics. Trainee doctors need more training on antimicrobial resistance (AMR). Standard treatment guidelines are either lacking or may have been developed by different authorities for the same conditions. These guidelines only partially fulfil the World Health Organization (WHO) recommendations. Consensus on treatment recommendations, tailored to local environments, is the need of the hour.

Vaccination reduces infections and the volume of antibiotics consumed due to both appropriate treatment of bacterial infections and inappropriate treatment of viral infections

The sale of antibiotics without a prescription is prohibited under Schedule H1, which has been supported by the red line campaign. But it is not widely enforced. Antibiotics continue to be easily accessible and self-medication rates are 73 per cent in some parts of India. The lack of access, due to geographical distance or affordability, to medical professionals and prescribers, in rural areas of India, leads 50 per cent of people to buy antibiotics directly from the pharmacy as a first choice.

Fixed dose combinations (FDCs) of two or more antibiotics, which have not been proven to be of greater benefit, and may have a greater risk of harm than therapies containing a single antibiotic. Between 2011 and 2012, 34 per cent of the total antibiotics sold in India were FDCs. More than a third

of FDCs sold in the same year were of unapproved formulations and 64 per cent of the 118 systemic antibiotic FDC formulations for sale in India were unapproved. In 2018, 328 FDC products were banned by the Central Drugs Standard Control Organization, though in the past such bans have been challenged by the industry. This has shown the ability of the government to effectively regulate antibiotics and reduce the risk posed by AMR.

Selection of antibiotics

Not only the quantity of antibiotic prescribed, but the selection of which antibiotic has a role to play in promoting drug resistance. Broad spectrum antibiotics target a larger range of bacteria and are more likely to select for resistance. WHO has categorised antibiotics into "Access", which should be widely available; "Watch", to be limited to specific indications; and, "Reserve", to be used as a last-resort. In 2015, India had the highest consumption rate worldwide for oxazolidinones, which have been defined by WHO as "Reserve" antibiotics. Consumption of carbapenems, also "Reserve" antibiotics, has increased in some hospitals. Between 2010 and 2014, consumption of faropenem, a carbapenem antibiotic, increased by 150 per cent. In some facilities, "Watch" and "Reserve" antibiotics are more commonly in stock than "Access" antibiotics.

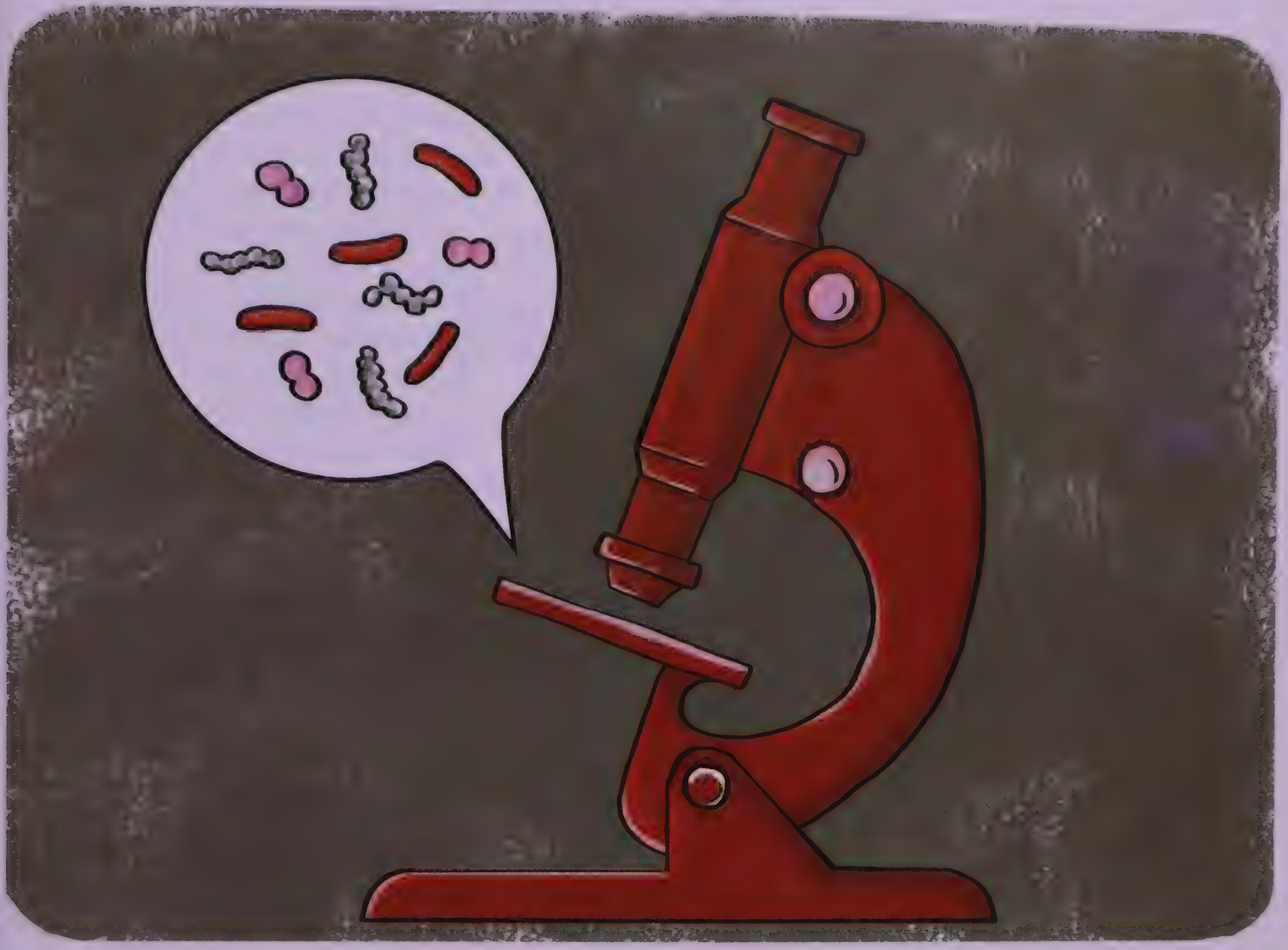
Evidence of hospital antimicrobial stewardship campaigns being effective in reducing consumption is encouraging. However, it also suggests some hospital prescriptions are inappropriate. Hospital drugs and therapeutics committees should be strengthened and healthcare providers should be trained in stewardship. Evidence from New Delhi suggests that private clinics prescribe antibiotics more often than public primary care settings. Given that 70 per cent of disease episodes are treated in the private sector, it is important to address inappropriate prescriptions in this sector.

When facilities run out of essential antibiotics, patients are forced to purchase them from uncertified vendors, which often charge higher prices and may have poorer quality stock. Falsified, substandard or counterfeit antimicrobials exacerbate AMR in several ways. They can leave patients under-dosed and bacteria that are only partially suppressed may be more likely to evolve resistance. This also prolongs the time during which the infection may be transmitted, facilitating the spread of resistant strains and leading to further antibiotic use. When drugs don't work, physicians prescribe the next line of antimicrobials, making resistance more likely to emerge to second-line drugs.

Multidrug-resistant tuberculosis affecting Tibetan refugees in India has been associated with the administration of counterfeit medicines and delayed treatment. Ciprofloxacin resistance is also related to low-quality ciprofloxacin. Half of the 10 per cent of medications worldwide that are falsified are antimicrobials, and 78 per cent of falsified medications are found in Asia or Africa. More than three per cent of drugs tested at the Indian National Drug Survey (2016–2018) were not of standard quality and 0.0245 per cent were spurious.

To effectively manage the use of antibiotics and mitigate the emergence of resistance, surveillance data on antibiotic consumption and resistance are needed. Resistance and consumption vary at the hospital and

The Central Pollution Control Board, which does not have maximum residual limits for antibiotic residues in pharmaceutical effluents, is in the process of setting limits



community levels and the data required needs to be at the level at which prescribing occurs to be informative. Though WHO collects data on consumption and resistance through the Global Antimicrobial Surveillance System (GLASS), consumption data for India was unavailable in the last report. Resistance data is now being collected. To inform prescribing, local hospital level data is needed. However, the lab facilities are often not available.

Even with access to surveillance data, clinicians need access to affordable, rapid and accurate diagnostics to guide appropriate prescription. C-reactive protein, procalcitonin and film array assays are used as indicators of bacterial infections, for which antibiotics are likely to be an appropriate treatment in cases where bacterial cultures are not available.

However, particularly in rural areas, diagnostic facilities are often lacking. Diagnostic tests often cost more than the empirical treatment, and trained lab staff, facilities and consumables may not be available. Rapid diagnostic tests for malaria have proven effective in reducing the inappropriate consumption of antimalarials, but have been associated with increased consumption of antibiotics. Further research is needed to understand how to mitigate such knock-on effects. Innovative technical solutions are required to meet the need for new diagnostics—the longitude prize is one initiative rising to this challenge.

Antibiotics in the environment

Opportunities for the appropriate management of antibiotics occur throughout the supply chain—from manufacture

through to consumption. About 80 per cent of antibiotics sold by multinational pharmaceutical companies have been manufactured in India or China. Effluents from this process contain active antibiotics, resistant bacteria and resistant genes. They contaminate rivers, streams and wells, including waters which are used for drinking and bathing. This increases both the emergence of resistant bacteria in local populations and also their spread.

In addition, even at the low levels present in wastewater, antibiotics select for resistant bacteria. Contamination in areas where the antibiotic manufacturing industry operates has shown to increase selection for bacteria that are highly resistant, even to last-resort antibiotics, such as the carbapenems.

At present, the Central Pollution Control Board does not have maximum residual limits for antibiotic residues in pharmaceutical effluents. However, this has been addressed and limits may be released soon. One objective of the Indian National Action Plan (NAP) on AMR is to develop such standards, however these are yet to be announced. To ensure that access to effective antibiotics is maintained, sustainable antibiotic production methods need to be developed and adopted by manufacturers.

Another source of environmental contamination is contaminated hospital waste. At 44 per cent, the Southeast Asia region has the lowest levels for safe health waste disposal. Untreated hospital waste may contain antibiotics and resistant bacteria. Where disposal mechanisms are inadequate, such waste puts staff and patients at increased risk from AMR. Water sources that become contaminated may cause infections to increase, and the associated antibiotic use is also likely to select for AMR. Investment in the infrastructure associated with appropriate waste disposal and the training of personnel are urgently needed.

The use of antibiotics for growth promotion in otherwise healthy animals is a common practice in India, as is across the world. In 2010, India was the fifth largest consumer of antibiotics in livestock (poultry, cattle, and pigs). It is projected that antibiotic use in this sector will grow by 312 per cent by 2030.

Antimicrobial residues have been found in chicken meat and shrimp being sold for human consumption. The use of Colistin in food-producing animals was recently banned in India. However, it remains to be seen how this will be enforced. A one health approach that incorporates diverse stakeholders from farming, veterinary, medical, and environmental sectors is essential to mount an effective response to AMR.

India, home to 17 per cent of the world population, has an important role to play in addressing AMR both in the South Asia region and on the global stage. At present, many more still die worldwide due to a lack of access to antibiotics than from resistant infections. However, in the long-term, for these drugs to remain effective, measures are needed to prevent the spread of resistance.

As India rolls out the universal health coverage, in the form of Ayushman Bharat, it will be important for access to be balanced with excessive and inappropriate use. In particular, where the administration of antibiotics appears to be a cheap alternative to investing in the infrastructure required for adequate infection prevention, which played a key role in the dramatic reductions in incidence of infectious diseases seen in the developed world.

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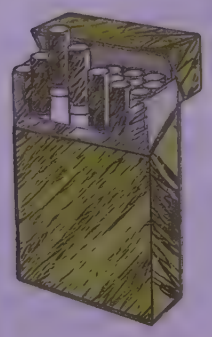
Be smart, use less

VIBHA VARSHNEY lists ways to reduce the need for antibiotics



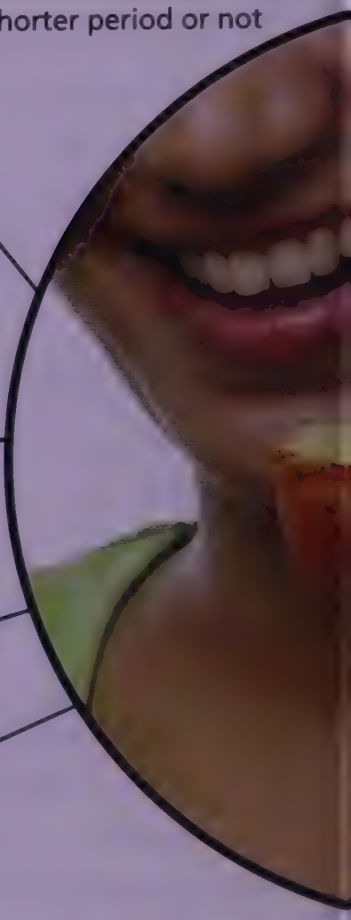
3 PROMOTE BREASTFEEDING

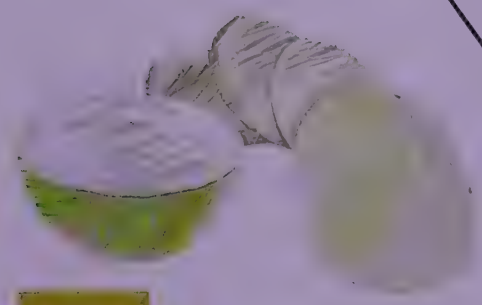
Breast milk boosts immunity. It has been observed that infants breastfed for at least six months had fewer resistant bacteria in their gut than babies who were breastfed for a shorter period or not at all.



2 STOP SMOKING

Cigarette smoke makes Methicillin-resistant *Staphylococcus aureus* (MRSA) more resistant to antibiotics and makes it more invasive and persistent. Exposure to cigarette smoke increases the rate of mutation in microbial DNA, resulting in microbes that are resistant to antibiotics.





1 CONSUME PROBIOTICS

Including probiotics in diet can help. It was seen that when infants and children consumed foods rich in bacterium like *Lactobacillus* and *Bifidobacterium*, they were at least 29 per cent less likely to need antibiotics.



10 GET VACCINATED

Vaccines can reduce the chances of contracting bacterial diseases and reduce the need for antibiotics. Where efficacy is proved, such vaccines should be used.



9 EMBRACE PROPHYLACTIC FOODS

High-fiber foods like whole grains, beans, fruits and vegetables help the growth of healthy bacteria in the gut. They should be eaten after taking antibiotics. As a precaution, these high fiber foods should not be consumed while taking the antibiotics as this reduces the absorption of the drug.



4

SUPPORT SAFE PREGNANCIES

Antibiotics should be avoided during pregnancy. It has been observed that number of antibiotic resistant bacteria in an infants gut are higher if their mother consumed antibiotics during pregnancy. Even breast milk of these mothers had resistant bacteria which can be passed on to the child.



5

EMBRACE NEW TECHNOLOGY

New technologies that can help reduce exposure to antibiotics are being developed. For example, tiny amounts of antibiotics embedded in corn-based nanoparticles help reduce the amount of antibiotic required. This also protects the microbiome in the intestines.





6

KEEP THE HOUSE DUST FREE

Presence of antimicrobial substances such as triclosan in indoor dust can make microbes resistant. This chemical is used in many consumer products such as toothpaste and hand washes and persist in the environment.



8

AVOID FOODS THAT REDUCE THE ACTIVITY OF ANTIBIOTICS

Fruit juices, dairy products or alcohol reduce the body's ability to absorb drugs. Maintain a gap of up to three hours eating these and antibiotics.



7

CONSUME FOODS THAT PROMOTE THE ACTIVITY OF ANTIBIOTICS

Some foods like honey, garlic, mushrooms, onions and spices like turmeric have antibiotic properties and should be consumed regularly to reduce chances of falling sick. Molecules derived from cranberry fruits is said to increase the sensitivity of pathogenic bacteria to antibiotics.

MICROBE MATRIX

Microbes will always triumph over antibiotics. We have to choose to fight the battles that will make a difference

RAKESH KALSHIAN

AS A species, we have evolved into killing machines extraordinaire. For us, killing is not just a matter of self-preservation, an instinct shared by all creatures that defend themselves with whatever weapons nature has blessed them with—poison, horns, incisors or claws. Armed with a supernatural arsenal, we now don't merely disable or kill; we aim to annihilate, be it termites, weeds, mosquitoes, cancer cells, or, going by Trump's "fire and fury" bluster, even fellow human beings.

Antibiotics are part of that arsenal and were designed to annihilate bad bacteria. Whenever we fall sick, doctors order them as a matter of routine. We are duly advised to complete the course, which usually lasts in multiples of five to seven days, lest some bacteria survive the attack, and mutate, thereby becoming immune to the drug. Not sticking to this dogma, according to the medical establishment, is one of the reasons behind the crisis of antibiotic resistance.

Intriguingly, it now turns out that this widely-held dogma has no scientific basis. In a recent edition of the *British Medical Journal*, medical researchers at Brighton and Sussex medical school claim that "the idea that stopping antibiotic treatment early encourages antibiotic resistance is not supported by evidence, while taking antibiotics for longer than necessary increases the risk of resistance." The heretics believe we are better off opting out the moment we feel better.

Resistance conundrum

This heresy does have some backers, but not yet large enough to inspire a paradigm shift and make doctors change tack. Meanwhile, the crisis of antimicrobial resistance (AMR) continues to spiral from grave to critical.

Apparently, the situation is so grim that researchers have painted apocalyptic visions of an "antibiotic winter" in which it will be almost impossible to do chemotherapy, organ transplants or C-sections, not to speak of treat deadly infections such as gonorrhea, meningitis, and typhoid. Last December, when news of bacteria resistant to the antibiotic colistin, apparently the last resort against multi-drug resistant bacteria, broke out, it filled researchers with dismay and dread.

Portents for India are particularly ominous as it is the world's largest consumer of antibiotics. According to a study published in *The Lancet*, in 2010, India consumed about 13 billion units, followed by China's 10 billion, and the US's almost 7 billion units. Worryingly, in the absence of rigorous studies and data, we don't even know how strong or large the enemy is.

As if this isn't scary enough, we have very little idea about how much antibiotics is consumed by the global dairy and meat industry. Apparently, China is an even greater offender—researchers believe that the bacteria strain resistant to colistin came from a Chinese pig farm. Even the EU, which outlawed this practice in 2006, is finding it



difficult to enforce the ban.

If we add to this toxic pool antibiotics that leak into drinking water as industrial and domestic effluents (treatment plants can't screen them), or those that leak into our meat and milk through farm animals, it would be fair to say that we are all dunked in a thick soup of antibiotics. Little surprise then Darwinian logic should kick in and select for resistance.

This sounds like a horror sci-fi movie in which antibiotics are made to appear almost like Trojan horses. And yet, about 75 years ago, when penicillin, the first antibiotic, was made, these wonder drugs were hailed as a panacea that would deliver humankind of all sorts of pestilences. Earlier, in the late 19th and early 20th century, germ theory—the outlandish idea that diseases were exploits of some wretched critters so small we couldn't even see them—inspired pioneers like Louis Pasteur, Joseph Lister and Robert Koch to take on bacterial scourges that had wiped out millions around the world. Between 1918 and 1919, the Great Spanish Flu engulfed 500 million people, and liquidated between 20 million and 40 million.

However, while this campaign did bring about a sanitation revolution, thereby erecting a first line of defense against an invisible enemy, scientists still had no idea about how to slay it once it had laid siege. They tried everything they could—poisons, dyes, and toxic metals—to spot and kill the bacteria, but in vain, until Alexander Fleming stumbled upon the bacteria-killing ability of common bread mould, out of which he extracted penicillin. Before long, scientists were farming antibiotics from fungi and bacteria, which

triggered the antibiotic revolution. Such was the euphoria about these wonder drugs that doctors believed they could cure almost any ailment without the collateral damage that went with many other potent medicines. So even as they saved millions of lives, indiscriminate and overzealous use eventually gave rise to phalanxes of mutant germs that defied ever-potent formulations.

Age-old tussle

Look at it this way. For millions of years, germs—bacteria, fungi, and algae—have been trying to outwit one another in a Darwinian struggle for existence. In this never-ending arms race, not only have they acquired chemical missiles called antibiotics, but they have also evolved self-defense strategies. In 2011, scientists stumbled upon 30,000-year-old bacteria lurking under permafrost in Canada's Yukon province that defied modern antibiotics, suggesting genes bestowing resistance to antibiotics have existed since ancient times.

Whenever we fall sick, doctors order them as a matter of routine and told to complete the course. It now turns out that this widely-held dogma has no scientific basis

So does this mean we are not guilty of inciting antibiotic resistance? Not entirely. As the American microbiologist Martin Blaser writes in his dystopian yet sobering *Missing Microbes*, "although resistance is ancient, we have made it a lot worse. We don't even know how many orders of magnitude…[but] even ocean life shows evidence of the spread of resistance from our activities." That antibiotic resistance is of ancient vintage also suggests that resistance is inevitable, and that any dream of a panacea against microbes is bound to shatter.

As worrisome as antibiotic resistance crisis is, some scientists believe that the abuse of antibiotics might even be behind the rise of modern plagues such as autoimmune disorders, juvenile diabetes, autism, obesity, food allergies, and a bunch of mysterious intestinal disorders, all of which defy scientific explanation. According to this hypothesis, such derangements happen when large colonies of innocuous bacteria are bumped off as collaterals in the scorched-earth assault of antibiotics. For, these bacterial swarms, which cover every millimetre of our bodies (picture this: against 30 trillion cells in the human body, there are about 100 trillion bacteria, collectively called the microbiome), inside as well outside, act as useful and efficient butlers performing key roles in the body's immune, metabolic, and cognitive faculties.

Clearly, the genie is out of the bottle, and it won't be easy putting it back in. Pharmaceutical companies do not want to invest in new antibiotics, as returns are only modest. Governments are doing their bit, like our own National Action Plan on AMR, to prevent the abuse of antibiotics through awareness campaigns, devising tests that can tell if a patient needs them, and hunt for new ones. However, given the scale and complexity of the AMR crisis, this may not be enough to inspire hope. For a start, governments can follow Denmark's example by eliminating antibiotics in the meat and dairy industry.

In any event, in the light of the legendary resilience of microbes, the least we can do is to keep them at bay by waging a limited war. As the evolutionary biologist Stephen Jay Gould put it: "We live in the Age of Bacteria (as it was in the beginning, is now, and ever shall be, until the world ends)…".

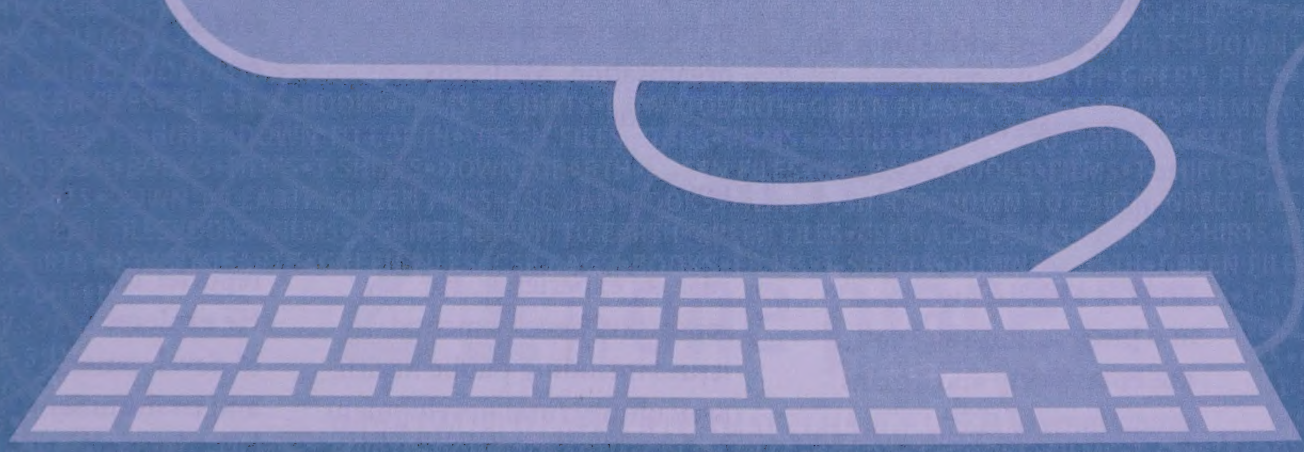
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Rarely—if ever—data on the exposure levels to toxic substances are known or made available to the public. There is a great need to empower communities by teaching them to conduct their own epidemiological surveys, specially given the State’s negative role in environmental issues.

ANIL AGARWAL
(1947-2002)

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